Is Vulvovaginal Lichen Planus Associated With Squamous Cell Carcinoma?

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Objective: The aim of the study was to assess for the presence of vulvar lichen planus (LP) in association with human papillomavirus (HPV)–independent squamous cell carcinoma (SCC).

Materials and Methods: We performed a clinicohistopathologic review of consecutive vulvectomy and wide local excisions for HPV-independent vulvar or vaginal SCC from 2007 to 2017. Data collected included site of SCC, adjacent precursor lesions and dermatoses, dermatologic treatment, and outcome.

Results: There were 43 cases of primary HPV-independent vulvar SCC treated by excision, but no vaginal cancers. Eighteen women (42%) had a preoperative diagnosis of lichen sclerosus (LS); none had a diagnosis of LP. Topical corticosteroids were prescribed in 19 (44%) of 43, with 4 women placed on maintenance therapy. Tumors arose from the labia minora, labia majora, and periclitoris, but not from vestibule or perianus. On histopathological review, LS was present in 41 (95%) of 43 specimens, whereas 1 had a nonspecific lichenoid reaction. On histologic review, 3 of 43 specimens, 1 had a nonspecific lichenoid reaction, and 1 had lichen simplex; both of the latter had subsequent biopsies showing LS. Lichen planus was not seen in association with SCC. Differentiated vulvar intraepithelial neoplasia (dVIN) was present in 38 (88%) of 43 specimens, whereas 1 had acanthosis with altered differentiation and 4 (9%) had no precursor lesion. Differentiated vulvar intraepithelial neoplasia had standard, basaloid, and hypertrophic morphology, superficially resembling erosive LP in 24 (54%) of 38 and hypertrophic LP in 6 (16%) of 38.

Conclusions: Lichen planus was not seen in association with HPV-independent vulvar SCC, whereas LS was underrecognized and inadequately treated in this group. Pathologists should be aware that dVIN may superficially resemble erosive or hypertrophic LP.

Key Words: lichen planus, lichen sclerosus, differentiated vulvar intraepithelial neoplasia, HPV-independent, vulvar squamous cell carcinoma

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There are 2 types of vulvar squamous cell carcinoma (SCC): approximately 30% of cases are human papillomavirus (HPV)–dependent and the other 70% are usually associated with lichen sclerosus (LS).1 Multiple studies suggest that vulvar SCC occurs in 5% of women with LS, and a recent prospective cohort study suggested that effective treatment mitigates this risk.2

Vulvovaginal lichen planus (LP) has also been described in association with vulvar neoplasia in several case reports and series, and SCC is occasionally noted in women with erosive LP during long-term follow-up.3,4 Limitations of this literature include lack of histopathologic confirmation of the LP diagnosis, inadequate follow-up, and failure to identify if neoplasia could be related to HPV or other carcinogens.3,4

The largest study to date reported 38 cases of LP-associated SCC and differentiated vulvar intraepithelial neoplasia (dVIN), occurring at a single European center.6 However, this series did not detail the histopathologic diagnostic criteria applied for the diagnosis of LP nor how LP was distinguished from LS and did not account for the possibility of comorbid LP and LS.7 A recent publication describes the difficulty in distinguishing the basaloid variant of dVIN from regenerative erosive LP, raising the question of neoplastic precursor lesions being mistaken for LP.8

The aims of this study are to assess consecutive excisions of primary HPV-independent vulvar and vaginal cancers for peritumoral LP, LS, and precursor lesions and to place these findings in the context of clinical diagnosis and management of SCC-associated vulvar dermatoses.

MATERIALS AND METHODS

The Pathology New South Wales Hunter New England database was searched for vulvectomy and excisions of vulvar or vaginal cancer submitted between 2007 and 2017 inclusive. Cases of recurrent cancer were excluded. Human papillomavirus–independent status was confirmed by routine histopathology and, when in doubt, through nonblock staining of p16 on adjacent VIN. Any case with previous or concurrent high-grade squamous intraepithelial lesion and/or positive p16 was excluded. The Hunter New England Research Ethics and Governance Unit approved this retrospective histopathologic case series (HREC 15/11/18/5.02), and signed written consent was obtained for use of clinical photographs.

Histopathologic review was performed of slides stained with hematoxylin and eosin (H&E). The tumor morphology was assessed as keratinizing or verrucous SCC. Verrucous SCC is a well-differentiated nonmetastasizing neoplasia with minimal suprabasilar nuclear atypia; spread occurs through an expansile blunt interface.9 The location of the tumor was determined through assessment of deep anatomic structures, site-specific stromal appendages, and the following perilesional epithelial types: squamous mucosa, mucocutaneous junction, hairless skin, and hair bearing skin. The peritumoral epithelium was then inspected for precursor lesions and adjacent dermatologic diseases.

Lichen sclerosus (LS) required basal layer degeneration seen as vacuolar change, apoptotic bodies, and/or squamatization, in combination with sclerosis or thick fibrosis of the papillary dermis and a closely applied band-like lymphocytic infiltrate.10 Squamatization is defined as a change in morphology of normal basilar keratinocytes to horizontally disposed cells with a mature squamous appearance.11 Classic LP required hyperkeratosis, hypergranulosis, sawtooth or spiky acanthosis, evidence of basal layer damage, a band-like lymphocytic infiltrate, and absence of dermal homogenization.12 Hypertrrophic LP required the changes...
of classic LP with superimposed lichenification seen as irregular elongated rete ridges and papillary dermal fibrosis.\textsuperscript{10,12} Erosive LP required epithelial thinning, often with erosion, a closely applied lymphocytic infiltrate, and either the degenerative or regenerative epithelial patterns.\textsuperscript{13} The regenerative pattern showed altered maturation, increased nucleus-to-cytoplasm ratio, and mitoses. Cases of a lichenoid pattern that lacked diagnostic features of LS or LP were labeled nonspecific lichenoid reaction.

Features of dVIN included a thickened hyperkeratotic or parakeratotic stratum corneum, acanthosis with elongated and branching rete ridges, premature maturation, enlarged squamous cells with large vesicular nuclei above the basal layer, and basal layer atypia characterized by the following 4 findings: increased mitoses, nuclear enlargement, pleomorphism, and hyperchromasia.\textsuperscript{13} We also looked for the basaloid variant of dVIN in which the epidermis is replaced by a homogenous population of abnormal keratinocytes.\textsuperscript{8,14} Basaloid dVIN was distinguished from regenerative erosive LP by the presence of marked nuclear pleomorphism, supported by an aberrant positive or negative p53; high-grade squamous intraepithelial lesion was excluded by a negative p16.\textsuperscript{6} Vulvar acanthosis with altered differentiation (VAAD) is a descriptive term for an unusual epithelial appearance with marked verruciform hyperplasia, plaque-like parakeratosis, hypogranulosis, a layer of pale-staining squamous cells, premature maturation, and absence of basal atypia.\textsuperscript{15} Vulvar acanthosis with altered differentiation was first described as a possible precursor lesion for verrucous SCC; alternatively, it may be associated with keratinizing SCC or may be a reactive phenomenon that resolves with treatment of the underlying dermatologic condition.

Clinical data collected included age, rurality, body mass index, diabetes mellitus status, tumor location and number, surgical stage, and outcome. Referrals and provider notes were reviewed for documentation of a clinical diagnosis of LS or LP occurring before cancer surgery. Additional data collected included previous and subsequent vulvar biopsies, treatment prescribed, and presence of a dermatologic diagnosis written on the pathology request form and in the histopathology report. Descriptive statistics were performed; clinical and histopathologic characteristics were compared with Fisher exact test.

**RESULTS**

There were 43 excisions for primary HPV-independent vulvar SCC; no vaginal cases were encountered. The mean age was 76 years, with 4 women 50 years or younger (Table 1). The diagnosis of LS was recorded in clinical notes before cancer surgery in 18 (42%) of 43, and there were no preoperative diagnoses of LP. There were no significant differences between women with and without a diagnosis of LS with regard to age, body mass index, diabetes status, rurality, notation of suspected or confirmed LS on the histopathology request form, surgical stage, and cancer outcome. A preoperative diagnosis was associated with postoperative documentation of LS (13/18 [72%] vs 7/25 [28%], \( p = .006 \)) but no significant difference in treatment. Topical corticosteroids prescribed were high potency in 11 (58%) of 19, medium in 6 (32%), and unspecified in 2 (11%). One woman was referred postoperatively to a vulvar specialist for LS management.

Tumor locations included labia minora, labia majora, and periclitoral; cancers did not originate at the vestibule or perianus. On review of excision specimens, LS was present in 41 (95%) of 43, and there were no preoperative diagnoses of LP. LS was present without a diagnosis of LS with regard to age, body mass index, diabetes status, rurality, notation of suspected or confirmed LP on the histopathology request form, surgical stage, and cancer outcome. A preoperative diagnosis was associated with postoperative documentation of LP (13/18 [72%] vs 7/25 [28%], \( p = .006 \)) but no significant difference in treatment. Topical corticosteroids prescribed were high potency in 11 (58%) of 19, medium in 6 (32%), and unspecified in 2 (11%). One woman was referred postoperatively to a vulvar specialist for LS management.

Tumor locations included labia minora, labia majora, and periclitoral; cancers did not originate at the vestibule or perianus. On review of excision specimens, LS was present in 41 (95%) of 43, 1 had a nonspecific lichenoid reaction, and 1 had lichen simplex chronicus; both of the latter had subsequent biopsies showing

| TABLE 1. Clinical Characteristics of Women With HPV-Independent Vulvar Cancer, Stratified by Preoperative Diagnosis of LS |
|---------------------------------------------------------------|
|                                | Total (n = 43) | Preoperative diagnosis of LS (n = 18) | No diagnosis (n = 25) |
| Age, mean (SD, range)          | 76 (12, 44–93) | 73 (11, 50–85) | 78 (12, 44–93) |
| Remoteness area, n (%)         |               |               |                |
| Metropolitan                   | 20 (47)       | 7 (39)        | 13 (52)        |
| Inner regional                 | 16 (37)       | 7 (39)        | 9 (36)         |
| Outer regional                 | 7 (16)        | 4 (22)        | 3 (12)         |
| BMI, mean (SD, range)          | 30 (8, 18–50) | 32 (7, 21–48) | 29 (7.8, 18–42) |
| Diabetes mellitus, n (%)       | 15 (35)       | 9 (50)        | 6 (24)         |
| Stage, n (%)                   |               |               |                |
| 0                              | 2 (5)         | 1 (6)         | 1 (4)          |
| 1                              | 28 (65)       | 13 (52)       | 15 (63)        |
| 2                              | 2 (5)         | 0             | 2 (8)          |
| 3                              | 9 (21)        | 3 (17)        | 6 (24)         |
| 4                              | 2 (5)         | 1 (6)         | 1 (4)          |
| LS suspicion or diagnosis on pathology request, n (%) | 10 (23) | 5 (28) | 5 (20) |
| LS documented postoperatively, n (%) | 20 (47) | 13 (72) | 7 (28) |
| Topical corticosteroids prescribed, n (%) | 15 (35) | 7 (39) | 8 (32) |
| Intermittent                   | 15 (35)       | 7 (39)        | 8 (32)         |
| Maintenance                    | 4 (9)         | 3 (17)        | 1 (4)          |
| Never                          | 24 (56)       | 8 (44)        | 16 (64)        |
| Outcome, n (%)                 |               |               |                |
| No evidence of disease         | 15 (35)       | 7 (39)        | 8 (32)         |
| Recurrence                     | 14 (33)       | 5 (28)        | 9 (36)         |
| Dead of disease                | 11 (26)       | 4 (22)        | 7 (28)         |
| No follow-up                   | 3 (7)         | 2 (12)        | 1 (4)          |
| Duration of follow-up, mean (SD, range), y | 3 (2, 1–8) | 2.9 (1.8, 1–8) | 3.1 (1.2, 1–8) |

HPV indicates human papillomavirus; BMI, body mass index; LS, lichen sclerosus.
LS (Table 2). There were no significant differences in tumor characteristics, precursor lesions, or histopathologic appearance of LS, when stratified by preoperative LS diagnosis. One woman who underwent excision of a right labial SCC with adjacent LS and dVIN had a concurrent punch biopsy of a noncontiguous perianal lesion that showed classic LP.

There were 3 morphologies of dVIN identified: standard, basaloid, and hypertrophic, and more than 1 type could be seen in the same specimen (see Figures 1–3). Of 38 cases with dVIN, 14 (37%) had a negative p16 to substantiate the HPV-independent diagnosis; this included all specimens with basaloid dVIN and 5 with standard morphology. Subepithelial sclerosis, the cardinal histopathologic feature of LS, accompanied dVIN in 72% of cases. Verrucous carcinoma and hypertrophic dVIN appeared as a spectrum of disease, rather than 2 distinct entities. Vulvar acanthosis with altered differentiation was more often seen in combination with dVIN than in isolation and was observed in cases both with and without verrucous SCC (see Figure 4). In addition to VAAD as described by Nascimento et al.,9 2 cases demonstrated other morphologies of “acanthosis with altered differentiation” seen as marked hyperkeratosis and hypergranulosis disproportionate to the acanthosis or as parakeratosis without the underlying pale band of squamous cells (see Figure 5). Those cases showed mild basal nuclear enlargement and occasional mitoses but lacked nuclear pleomorphism and hyperchromasia, so they did not fulfill criteria for basal atypia as seen in dVIN.

| TABLE 2. Histopathologic Characteristics of HPV-Independent Vulvar Cancer, Stratified by Preoperative Diagnosis of LS |
|---------------------------------------------------------------|
| **Total (n = 43)** Preoperative diagnosis of LS (n = 18) No diagnosis of LS (n = 25) |
| **Tumor origin, n (%)** |
| Periclitoral | 12 (28) | 2 (12) | 10 (48) |
| Labium minus | 18 (42) | 9 (50) | 9 (36) |
| Labium majors | 13 (30) | 7 (39) | 6 (24) |
| **Tumor histopathology, n (%)** |
| Keratinizing | 37 (86) | 16 (89) | 23 (92) |
| Verrucous | 2 (5) | 1 (6) | 1 (4) |
| Both | 4 (9) | 3 (17) | 1 (4) |
| **Tumors, n (%)** |
| 1 | 32 (74) | 12 (67) | 20 (80) |
| 2 | 6 (14) | 3 (17) | 3 (12) |
| ≥3 | 5 (12) | 3 (17) | 2 (8) |
| LS noted on pathology report | 33 (77) | 16 (89) | 17 (68) |
| Perilesional dermatosis on review of cancer excision, n (%) |
| LS | 41 (95) | 18 (100) | 23 (92) |
| Lichenoid, nonspecific | 1 (2) | 0 | 1 (4) |
| Lichen simplex chronicus | 1 (2) | 0 | 1 (4) |
| **Precursor lesion, n (%)** |
| None | 4 (9) | 1 (6) | 3 (12) |
| VAAD | 1 (2) | 0 | 1 (4) |
| dVIN | 34 (79) | 16 (89) | 18 (72) |
| dVIN and VAAD | 4 (9) | 1 (6) | 3 (12) |
| LS epithelium, n (%) |
| Normal | 14 (33) | 4 (22) | 9 (36) |
| Atrophic | 5 (12) | 3 (17) | 2 (8) |
| Lichenified | 22 (51) | 11 (61) | 12 (48) |
| Not applicable | 2 (5) | 0 | 2 (8) |
| LS stroma, n (%) |
| Hyalinized | 20 (47) | 10 (56) | 10 (48) |
| Fibrotic | 3 (7) | 1 (6) | 2 (8) |
| Hyalinized and fibrotic | 15 (35) | 6 (33) | 9 (36) |
| Hyalinized and edematous | 3 (7) | 1 (6) | 2 (8) |
| Not applicable | 2 (5) | 0 | 2 (8) |
| **Features of dVIN** (n = 38) (n = 17) (n = 21) |
| **Morphology, n (%)** |
| Standard | 23 (53) | 9 (53) | 14 (67) |
| Hypertrophic | 6 (14) | 4 (24) | 2 (9.5) |
| Basaloid | 4 (9) | 2 (12) | 2 (9.5) |
| Basaloid and other | 5 (12) | 2 (12) | 3 (14) |
| Stromal sclerosis, n (%) |
| 31 (72) | 16 (94) | 15 (71) |

HPV indicates human papillomavirus; LS, lichen sclerosus; dVIN, differentiated vulvar intraepithelial neoplasia; VAAD, vulvar acanthosis and altered differentiation.
The diagnosis of LS was written in 33 (77%) of pathology reports, but 14 (42%) of these cases never had a clinical diagnosis recorded. During postoperative follow-up, 8 additional women received diagnoses of LS by punch biopsy, 6 (75%) of whom were treated. Mean follow-up was 3 years (range = 1–8 years). Among 11 (26%) women who died of disease, the mean interval from diagnosis was 3.3 years. Eight (42%) of 19 women prescribed topical corticosteroids had no evidence of recurrent cancer during follow-up, compared with 7 (29%) of 24 of untreated women; this was not statistically significant.

**DISCUSSION**

For an 11-year period, 95% of excisions for HPV-independent vulvar SCC showed histopathologic evidence of LS. The other 5% had subsequent biopsies showing LS. There was no evidence of hypertrophic, classic, or erosive LP in the SCC specimens. These results suggest that vulvar SCC associated with LP is rare.

There are several reasons to doubt an association between vulvovaginal LP and SCC. Erosive LP is usually seen on nonkeratinized epithelium of vestibule and vagina, but primary HPV-independent vaginal cancer has not been reported and vestibular tumors are uncommon, although establishing an origin site medial to the mucocutaneous junction is difficult if there is dermatoysis-associated architectural change or the cancer is locally advanced. The proposed mechanism for LS-associated neoplasia is the scar-cancer hypothesis, in which the combination of altered epithelial-stromal interface and chronic epithelial damage and repair leads to accumulation of carcinogenic mutations.15,16 Classically, scar cancers arise from burns and chronic ulcers; in the case of LS, the scar is the band of abnormal stromal collagen and the damaged epithelium results from T-cell-mediated attack on basal keratinocytes.17 Lichen planus lacks significant scarring, and chronic inflammation alone is a weak potential driver for carcinogenesis. Finally, controversy continues regarding the malignant potential of oral LP, with that literature likewise afflicted by problems with clinical and histopathologic diagnoses, documentation of comorbidities, and inadequate follow-up. The mouth is a carcinogen-rich environment in which multiple pathways result in a common end point of atypical epithelium; toxic exposures may cause antigenic alterations in mucosal basal cells, triggering a secondary lichenoid reaction.4,17 In an effort to reduce the possibility of misattribution to LP, consensus criteria were constructed on diagnosis of oral lichenoid lesions.17 No similar criteria exist for vulvovaginal disease.

Pathologic assessment of peritumoral dermatoses and precursor lesions is challenging and presents many opportunities for misdiagnosis. Previous studies have documented that dVIN may be misdiagnosed as LS and that p53 overexpression can occur both in benign and neoplastic conditions.9,13,18,19 This study highlights several other pitfalls in assessment of these specimens. The basaloid variant of dVIN occurred in 21% of cancers and sometimes was the only precursor lesion present; clues to distinguish it from regenerative erosive LP include parakeratosis, minimal epithelial thickening, abnormal mitotic figures, and more nuclear hyperchromasia. The hypertrophic variant of dVIN was seen in 14% and is a mimic for hypertrophic LP; the presence of atypical nuclei away from the inflamed dermoepidermal junction is the major distinguishing characteristic. Another feature that may cause diagnostic confusion is pseudoepitheliomatous hyperplasia, a benign squamoproliferative condition that occurs within LCS.
LP, LS, and nodular prurigo, and histopathologically resembles SCC. Mistaking pseudoepitheliomatous hyperplasia for SCC leads to unnecessary surgical intervention and attribution of the purported cancer to the adjacent dermatosis. Finally, cases of LS with edematous, fibrotic, or localized collagen change may be misinterpreted as LP or a nonspecific lichenoid reaction. Distinguishing between LP and LS also presents difficulties to clinicians. The adage that LS is a disease of keratinized skin is incorrect as LS can extend into the vestibule and vagina and rarely may present as an isolated lesion in squamous mucosa. Hypertrophic LP and lichenified LS both demonstrate a combination of erythema and pallor, often accompanied by architectural change, erosions, excoriations, and superinfection. The diagnosis of comorbid LP and LS requires a high index of suspicion and is confirmed with 2 well-placed biopsies; thus, this phenomena is likely underreported. However, this study suggests that LS may be overlooked even when the clinical appearance is typical and peritumoral LS is noted on the pathology report. This is especially problematic because adjacent LS is associated with a three-fold risk of local recurrence of vulvar SCC and a five-fold risk of second field tumors. In contrast, margin status is not related to HPV-independent SCC recurrence risk.

Despite recent evidence to suggest that a tailored long-term regimen of topical corticosteroids reduces the risk of primary vulvar cancer, only 4 women in this high-risk group were ever prescribed maintenance therapy. Heterogeneity in international clinical guidelines likely contributes to a laissez-faire approach to long-term surveillance and treatment of LS. European guidelines state that “maintenance treatment with either topical steroids or calcineurin inhibitors is recommended as it seems to prevent severe relapses” and that frequency of steroid application is determined by symptoms. British guidelines restrict maintenance treatment to women with persistent symptoms or appearance of active disease, with follow-up annually by a general practitioner for stable disease and specialist opinion for “atypical or poorly controlled” disease or previous neoplasia. North American guidelines state that the evidence for maintenance therapy is conflicting and do not discuss referral to vulvar specialists. Australian guidelines have recently been updated to advise chronic regular use of a topical corticosteroid potent enough to maintain remission and that management should be in consultation with an expert. None of these documents specifies the role of gynecologic oncologists in management of vulvar dermatoses; moreover, there is no mention of LS treatment in national oncologic guidelines for management of vulvar cancer. Most gynecologic oncologists have limited training and experience in long-term care of dermatoses, so involvement of a vulvar specialist in the follow-up of women with dVIN and HPV-independent SCC could offer advantages both in quality of life and reduced recurrence rates, with research urgently needed to assess this hypothesis.

This study adds to the literature on the relationship between keratinizing SCC, verrucous SCC, and VAAD. The acronym “VAAD” was devised as a descriptive term for an unusual acanthotic lesion that lacks the basal atypia of dVIN and is remarkable for plaque-like parakeratosis with conspicuous underlying pallor; it was originally described as a precursor to verrucous SCC but has since been identified with keratinizing SCC. We observed variants of “acanthosis with altered differentiation”...
in cancer excision specimens that do not fulfill all criteria of the original VAAD description and agree that the nomenclature and definition should be revised to accommodate the various manifestations of this maturation abnormality. The potential for reversibility of these lesions with aggressive treatment of the underlying dermatosis remains unclear. We found no clear histopathologic distinction between hypertrophic dVIN and verrucous SCC, and 4 (9%) of 43 cases showed coexistent verrucous and keratinizing SCC. Previous histopathologic studies of both vulvar and oral verrucous SCC specimens demonstrate foci of atypia or invasion consistent with conventional SCC in 20% to 35%; this is a high rate of comorbidity if these were synchronous-unrelated primaries.

From a clinical perspective, women with verrucous SCC have a substantial risk of concomitant or subsequent keratinizing SCC and should be managed similarly to women with dVIN.

Inherent to the retrospective design, limitations of this study include incomplete data, practice differences between clinicians, and the potential for selection bias. This study did not capture advanced vulvar or vaginal cancers confirmed by an external biopsy and referred directly for chemoradiation. Inherent to the retrospective design, limitations of this study include incomplete data, practice differences between clinicians, and the potential for selection bias. This study did not capture advanced vulvar or vaginal cancers confirmed by an external biopsy and referred directly for chemoradiation.

In summary, LP was not encountered in excision specimens for vulvar SCC occurring for more than a decade. Lichen sclerosus was histopathologically demonstrated in association with all HPV-independent SCC cases, either adjacent to the tumor or at a subsequent vulvar biopsy. Therefore, a high rate of comorbidity if these were synchronous-unrelated primaries.

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