Anogenital High-Grade Squamous Intraepithelial Lesion Comorbid With Vulvar Lichen Sclerosus and Lichen Planus

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Objective: The aim of the study was to describe the clinicopathologic features of vulvovaginal or anal high-grade squamous intraepithelial lesion (HSIL) comorbid with lichen sclerosus and/or lichen planus (LS/LP).

Methods: The local pathology database identified 37 consecutive cases from 2007 to 2019 of vulvar, vaginal, or anal HSIL among women who had a histopathologic diagnosis of vulvar LS/LP. Cases had p16 and p53 immunoperoxidase stains. Clinical data included age, relative location of HSIL and LS/LP, immune-modifying conditions, tobacco use, treatment type, and follow-up. Histopathologic data included HSIL morphology categorized as warty-basaloid or keratinizing, p16 and p53 patterns within HSIL, and features of LS/LP.

Results: The mean age was 69 years with a median follow-up up 42 months. Lichen sclerosus, alone or in combination with LP, was the comorbid dermatosis in 89%. Lichen sclerosus/lichen planus was overlapping or adjacent to HSIL in two-thirds of cases and located separately in the remainder. Rates of tobacco use and immunologic dysfunction were each 40%. In cases of co-located LS and HSIL, sclerosis was absent under the neoplasia in 57%. Twenty-four percent of HSIL cases showed keratinizing morphology; block-positive p16 and suprabasilar-dominant p53 helped distinguish HSIL from human papillomavirus–independent neoplasia.

Conclusions: Histopathologic identification of comorbid HSIL and LS/LP may be challenging because of keratinizing morphology and loss of diagnostic features of LS. Clinicopathologic correlation and use of p16 and p53 are essential to achieve an accurate diagnosis and enact disease-specific management plans.

Key Words: lichen sclerosus, lichen planus, vulva, vagina, anus, high-grade squamous intraepithelial lesion, usual vulvar intraepithelial neoplasia, differentiated vulvar intraepithelial neoplasia, HSIL, uVIN, dVIN, p16, p53, sclerosis

(*J Low Genit Tract Dis* 2020;24: 311–316)

Vulvar squamous cell carcinoma (SCC) comprises 2 distinct entities. More than 60% of cases are HPV independent, usually arising from differentiated vulvar intraepithelial neoplasia (dVIN) in association with lichen sclerosus (LS), and the remainder are human papillomavirus (HPV)-related with high-grade squamous intraepithelial neoplasia (HSIL) as a precursor.[1–3] However, LS and lichen planus (LP) sometimes coexist with HPV-related disease of the lower genital tract (LGT).[4–6] A cohort study of Italian women with vulvar HSIL (usual VIN, uVIN) found clinical diagnoses of LP in 3% and LS in 7%, and HSIL was more likely to recur in women with comorbid LP.[5] There is scant information about the demographics, presentation, pathologic assessment, and management of these cases. This study aims to describe the clinical and histopathologic features of 37 consecutive cases of biopsy-proven HSIL comorbid with LS and/or LP (LS/LP) and identify mechanisms to assist with diagnosis.

METHODS

The Pathology New South Wales Hunter New England database was searched for biopsies and excisions of vulvar, vaginal, or anal HSIL from January 2007 to March 2019, among women with a histopathologic diagnosis of LS/LP. The Hunter New England Research Ethics and Governance Unit granted approval for this study (HREC 15/11/18/5.02), and written consent was obtained for publication of clinical photographs. Inclusion required histopathologic confirmation of both HSIL and LS/LP.

The diagnosis of LS required basal layer degeneration seen as vacuolar change, apoptotic bodies, and/or squamatization, in combination with sclerosis or fibrosis of the papillary dermis.[7,8] A band-like lymphocytic infiltrate was supportive but not required, because of the possibility of treatment effect or disease inactivity. Erosive LP required epithelial thinning, often with erosion, a closely applied lymphocytic infiltrate, and a degenerative and/or regenerative epithelial pattern.[9] When features supported but did not confirm a lichenoid dermatitis, the case was excluded.

Diagnosis of HSIL required cellular atypia, defined as nuclear enlargement, hyperchromasia, pleomorphism, and increased and/or abnormal mitoses. High-grade squamous intraepithelial lesion morphology was categorized as warty-basaloid or keratinizing.[10,11] Warty-basaloid HSIL demonstrates replacement of more than half of the epithelium with atypical basaloid cells with a large nucleus-to-cytoplasm ratio and a small amount of basophilic cytoplasm. Keratinizing HSIL shows atypia confined to the lower half of the epithelium and suprabasilar maturation. Areas of HSIL were inspected for simultaneous features of LS/LP, to include basal layer degeneration and collagen abnormalities.

All specimens had standard hematoxylin and eosin (H&E) and periodic acid–Schiff stains plus immunoperoxidase for p16, a marker of transforming HPV infection and a reliable indicator of an HPV-related process.[1–3,10–12] Block-positive p16, defined as strong diffuse nuclear and cytoplasmic staining over the lower half of epithelium, was considered confirmatory of HSIL. Nonblock-positive cases with a strong clinicopathologic suspicion of HPV-related disease had genotyping using an L1 primer, with positive cases receiving type-specific assessment. Immunoperoxidase for p53 was obtained on stored tissue blocks, of which 3 were unavailable. Several authors describe a distinctive p53 pattern in HSIL that spares the basal layer; in this study, p53 staining was documented descriptively to validate or refute those observations.[13,14] Specimens with nuclear atypia, negative or nonblock-positive p16, and basal-overexpressed, null, or wild-type p53 were classified as dVIN and excluded from this study. Other exclusion criteria were negative tissue HPV genotyping,

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The authors have declared they have no conflicts of interest.

This study was approved by the Hunter New England Research Ethics and Governance Unit (HREC 15/11/18/5.02).

Written permission was provided for publication of clinical photos.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jlgtd.com).

DOI: 10.1097/LGT.0000000000000540

second opinion cases from outside facilities, and nonconfirmation of the original diagnoses.

Clinical data included age, diabetes mellitus (DM), autoimmune disease, immune-modulating medications, tobacco use, treatment type, and duration of follow-up. Clinical and pathology records were searched for evidence of HPV-related disease elsewhere, to include high-risk HPV at the cervix or vagina, previous cervical excisional procedures, and hysterectomy for HSIL. A previous or subsequent diagnosis of dVIN or vulvar SCC was noted. Lichenoid and neoplastic processes were classified as separate or co-located based on descriptions, schematics, and photographs of clinical appearance; cases with uncertainty about relative location were further informed by histopathologic reassessment of the adjacent epithelium. The data were analyzed with descriptive statistics and group comparisons with Fisher exact test.

RESULTS

One hundred twenty-three specimens from 37 women met inclusion criteria. The mean age was 69 years (59–88 years) with a median follow-up of 42 months. The median number of specimens was 3, with a range of 1–9. Lichen sclerosus, alone or in combination with LP, was the comorbid dermatosis in 33 women (89%), and all LP cases were erosive type (see Table 1). High-grade squamous intraepithelial lesion and LS/LP were overlapping or adjacent in two-thirds of cases. Two women had HSIL confined to the anus or vagina, 3 had exclusively perianal disease, and the remainder had vulvar HSIL often described as multifocal (n = 8, 22%) or at labia minora (n = 16, 43%). Complete clinical data were missing for 2 cases.

TABLE 1. Clinical Characteristics of Comorbid HSIL and LS and/or LP

	N = 37
Age, mean (range; SD)	69 (59–88; 12)
Comorbid disease with HSIL, *n* (%)	
LS	27 (73%)
LS and erosive lichen planus	6 (16%)
Erosive lichen planus	4 (11%)
Location of HSIL and LS/planus	
Overlapping and/or adjacent	24 (65%)
Separate	13 (35%)
Full clinical data available, *n = 35*	
Follow-up months, median (range)	42 (0–204)
Tobacco, current or former, *n* (%)	14 (40%)
DM or immunologic dysfunction, *n* (%)	14 (40%)
HPV-independent neoplasia[a]	6 (17%)
HPV-related disease elsewhere in LGT, *n* (%)	19 (54%)
HPV DNA at cervix or vagina, *n* (%)	
HPV 16/18	6 (17%)
HPV other	2 (6%)
Negative	8 (23%)
Untested/unknown	19 (29%)
Topical corticosteroid for dermatoses	
Potent	13 (37%)
Weak	6 (17%)
Unspecified	12 (34%)
Nil prescribed	4 (11%)
Treatment of vulvar HSIL[b]	
Surgical	33 (94%)
LASER	11 (31%)
Imiquimod	3 (9%)

[a]Includes squamous cell carcinoma and differentiated vulvar intraepithelial neoplasia.

[b]Treatments were multimodal for some patients.

Differentiated VIN or HPV-independent SCC occurred before or subsequently to diagnosis of HSIL in 6 (17%). Human papillomavirus-related vulvar SCC occurred in an additional 4 (11%); 3 were microinvasive. Nineteen (54%) of 35 patients had current or previous HPV-related disease elsewhere: 1 cervical microinvasive SCC, 1 adenocarcinoma-in-situ, 8 cases of cervical or vaginal HSIL, 7 of low-grade squamous intraepithelial lesion or condyloma, and 2 of unspecified cervical disease. Twenty-eight (76%) of women had histopathologic diagnosis of LS/LP before HSIL, 4 (11%) had a long-standing clinical LS with histological confirmation occurring after identification of HSIL, 3 (8%) had a new diagnosis of LS during HSIL surveillance, and 2 (5%) referred for vulvar pruritus and had simultaneous diagnoses of comorbid disease.

Tobacco use (40%) and immunologic dysfunction (40%) were common, with the latter comprising 4 with DM, 3 with autoimmune thyroid disease, 3 with rheumatoid arthritis, 2 with celiac disease, 2 with splenectomy, and 1 each with scleroderma, systemic lupus erythematosus, vonWillibrand disease, Raynaud syndrome, and recent treatment for small bowel melanoma. Several women had more than one of these, and an additional 2 received treatment for hepatitis C.

A spectrum of appearances was consistent with HSIL. Clinical impressions included LS/LP in 12 (32%), VIN in 9 (24%), LS with VIN in 9 (24%), SCC in 5 (14%), hemorrhoids in 1, and eczema in 1. In cases identified as VIN, clinicians attempted to categorize these as uVIN or dVIN in 5 (28%) of 18. A well-demarcated glazed red patch abutting LS was initially considered erosive LP (see Figure 1). White plaques on a background of abnormal skin were described as lichenified LS versus dVIN (see Figure 2A). An exophytic verruciform lesion with variable color and texture provoked concern for SCC (see Figure 3A).

Excision was the only treatment modality undertaken in 60%. Ten women (28%) had multimodal therapy, with imiquimod used only as an adjunct to LASER or excision (see Table 1). Topical corticosteroid was prescribed for management of LS/LP in all but 4 women, but the potency was either weak or unspecified in 51%. Follow-up was subspecialist led in 31 (84%), whereas 4 did not return despite advice and 2 were transferred to primary care.

High-grade squamous intraepithelial lesion had keratinizing morphology in 19% of specimens; an additional 2 (5%) cases had both keratinizing and warty-basaloid HSIL from specimens obtained at different times (see Table 2; Figures 2, 4). The relative location of LS/LP did not seem to influence the epithelial appearance of HSIL. The age range of women with warty-basaloid HSIL was 42–87 years, whereas keratinizing morphology occurred only after age 60 years. Of 23 cases of HSIL overlying or adjacent to LS, 10 (43%) demonstrated sclerosis underneath the neoplastic process (Supplemental Figure 1, http://links.lww.com/LGT/A161). Dermal sclerosis sometimes remained consistent across the 2 diseases but also was seen to disappear as the epithelium changed from LS to HSIL (see Figure 3). There were 5 (14%) cases in which basal layer features of LS were preserved within an area of HSIL.

The p53 pattern in HSIL was suprabasilar dominant, with variable strength and rate of nuclear staining across cases (see Figures 2E, 3D, 4C; Supplemental Figures 1C, 2B, D, http://links.lww.com/LGT/A161, http://links.lww.com/LGT/A162). Two cases had strong clinicopathologic suspicion for HSIL but a

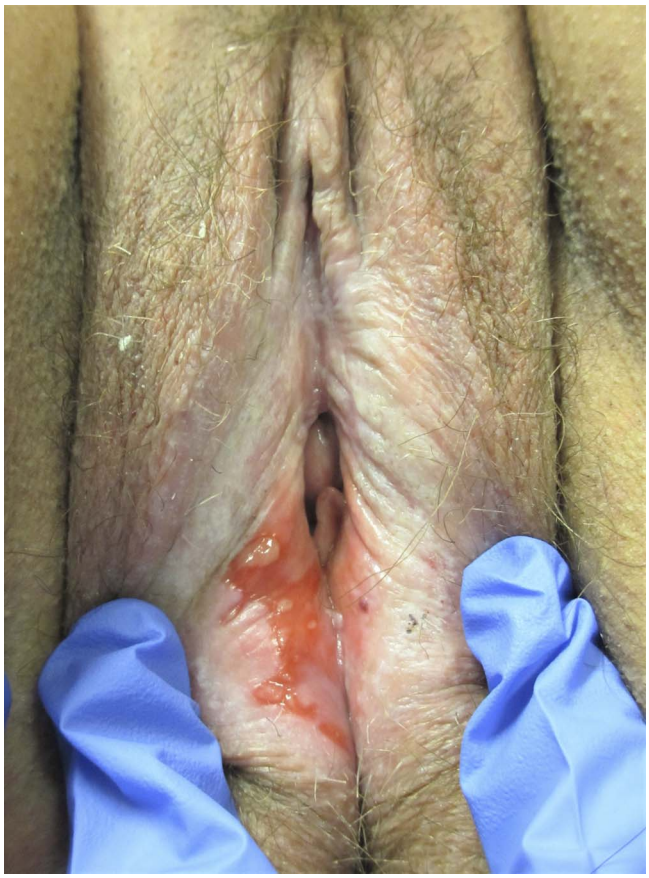

FIGURE 1. Warty-basaloid HSIL and LS: a well-demarcated glazed red patch on right labium minus (HSIL) abutting circumferential pallor and lichenification (LS).

nonblock-positive p16; 1 showed patchy nuclear and weak cytoplasmic staining, the other had strong diffuse cytoplasmic and focal nuclear staining (see Supplemental Figure 2, http://links.lww.com/LGT/A162). Both women were former tobacco users; 1 had vaginal and vulvar lesions (see Supplemental Figures 2A, B, http://links.lww.com/LGT/A162), and the other had a single episode of uVIN separate from LS/LP with no recurrence after excision and cessation of Plaquenil (see

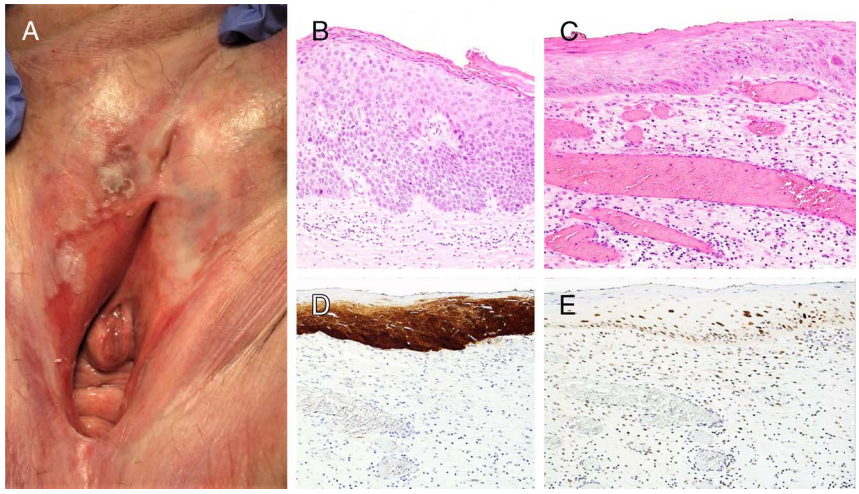

FIGURE 2. High-grade squamous intraepithelial lesion, LS, and erosive LP: A, white papules and plaques (HSIL) at the right-sided interface between circumferential pallor (LS) and a vestibular glazed red patch (LP), accompanied by vulvar architectural change, (B) warty-basaloid HSIL with dermal fibrosis, H&E ×200, (C) keratinizing HSIL with parakeratosis, premature maturation, and atypia seen at the basal and suprabasal layers, H&E ×200, (D) block-positive p16, and (E) suprabasilar-dominant p53.

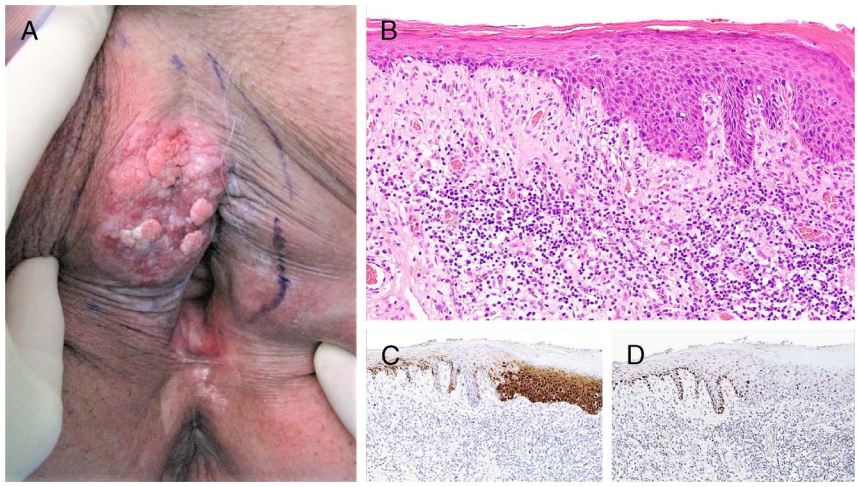

FIGURE 3. A, Warty-basaloid HSIL and LS: exophytic verrucous plaque with variable color and texture (HSIL) on a background of pallor, LS, and architectural change (LS), (B) LS loses its sclerosis in the area replaced by HSIL, H&E ×100, (C) block-positive p16 in HSIL with focal staining in LS, and (D) basal-overexpressed p53 in LS contrasts with suprabasilar-dominant staining in HSIL.

Supplemental Figures 2C, D, http://links.lww.com/LGT/A162). In both, HPV 16 DNA was identified in excised tissue.

DISCUSSION

Assessment and management of women with comorbid HSIL and LS/LP may be challenging. Symptoms range from absent to severe and examination is often complicated by adjacent and overlapping disease processes, multiple morphologies, secondary features like excoriation, mycotic, or bacterial superinfection, and superimposed dermatitis.[6,8,9,15–17] Tobacco use and immune dysfunction are common comorbidities and serve as targets for primary or secondary prevention efforts. Careful surveillance and frequent biopsy are mechanisms to overcome these difficulties.[4–6]

There are 3 major differential diagnoses for atypical nuclear features in vulvar epithelium: HSIL, dVIN, and reactive change. If histopathologic assessment is limited to standard H&E and periodic acid–Schiff, some cases will be misclassified. Keratinizing HSIL is a mimic for dVIN because both display basal atypia accompanied by epithelial maturation.[8,10] The 24% rate of keratinizing HSIL found in this study is higher than the 5% previously documented in uVIN.[10,11] Women with comorbid HSIL and LS/LP are likely older and sicker than those included in larger studies of vulvar HSIL, but the relationship between age, comorbidities, and epithelial morphology remains unclear. At the other end of the morphologic spectrum, full-thickness abnormal cells usually indicate warty-basaloid HSIL, but this pattern is also seen in basaloid dVIN and regenerative erosive LP.[9,18,19] Although block-positive p16 permits categorization of most cases into HPV related or HPV independent, false-positives and false-negatives occur and transforming HPV infection is not interchangeable with a diagnosis of HSIL.[10,12,20,21] A nonblock-positive p16 staining pattern has been documented in 5% of cervical HSIL, and this may be extrapolated to other LGT sites.[21] In addition to test limitations, up to 5% of cases remain unclassifiable after H&E and p16 assessment.[10,18]

This study suggests that p53 compensates for the limitations of microscopy and p16 and is valuable when attempting to distinguish between HSIL, dVIN, and reactive change. The p53 pattern in HSIL is suprabasilar dominant, presenting a dramatic contrast

TABLE 2. Histopathological Characteristics of Comorbid HSIL and LS and/or Lichen Planus

	N = 37	HSIL and LS/LP overlapping or adjacent, *n* = 24	HSIL and LS/LP separate, *n* = 13
Features of HSIL			
HSIL morphology			
Warty-basaloid	28 (76%)	18 (75%)	10 (77%)
Keratinizing	7 (19%)	4 (17%)	3 (23%)
Both	2 (5%)	2 (8%)	0
Basal layer damage present within HSIL	5 (14%)	5 (21%)	0
p16 staining			
Block-positive	35 (95%)	23 (96%)	12 (92%)
Nonblock-positive	2 (5%)	1 (4%)	1 (8%)
Dermal sclerosis in HSIL, *n* = 33[a]			
Present	10 (30%)	10/23 (43%)	0
Absent	23 (70%)	13/23 (57%)	10 (100%)

[a]Where HSIL was comorbid with LS.

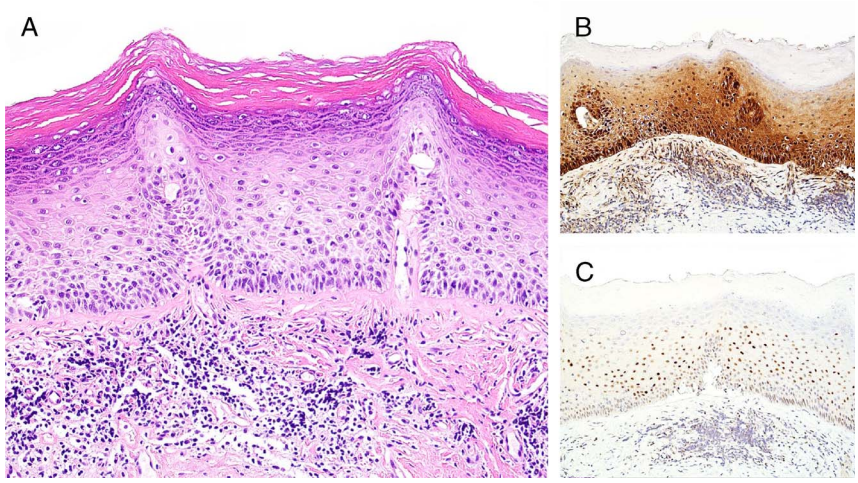

FIGURE 4. A, Keratinizing HSIL with well-keratinized epithelium and crowded atypical nuclei at the basal layers, H&E ×200, (B) block-positive p16, and (C) suprabasilar-dominant p53.

to basal overexpressed or null patterns of dVIN and the basal overexpressed or wild-type patterns of reactive change.[22] p53 has often been reported as either negative/wild type or positive.[10,23] However, several authors have specified a distinctive p53 appearance in uVIN—an "accentuated… pattern [that] spared the basal layer" and "suprabasal positivity… occasionally showed a distinct clustered pattern in which central… rete ridges were positive… whereas the rest of the epithelium was negative."[13,14] Replication of those findings lends strength to the recommendation that a tandem panel of p16 and p53 is essential in assessment of VIN comorbid with LS/LP.[13] Discordance between p16 and p53 presents a conundrum in the determination of HPV-independent versus HPV-related neoplasia. A mixed carcinogenic etiology may be responsible for rare lesions that arise out of LS, show keratinizing morphology, and have block-positive p16 in combination with basal overexpressed or null p53. In absence of molecular profiling, the safest approach for difficult-to-classify lesions is to treat as if they are dVIN: excise with clear margins and institute surveillance focused on optimal management of comorbid LS/LP with biopsy of treatment-resistant areas.

The pathologic assessment of co-located HSIL and LS presents several additional challenges. When epithelial morphology is keratinizing and accompanied by sclerosis, the immediate impression may be LS and neoplasia may be missed.[12] Evaluation of any treatment-resistant lesion arising in LS requires careful assessment for basal layer atypia and recognition, and this may be either type of VIN. The other difficulty is identification of LS when dermal sclerosis has disappeared underneath HSIL. Sclerosis is the defining characteristic of LS; in its absence, the pathologist will report the neoplastic process and not realize that it occurs on a background of LS. Inspection of adjacent and distant nonneoplastic epithelium for sclerosis and basal layer damage may allow for diagnosis of the comorbid LS. Marked fibrosis underneath HSIL also favors a diagnosis of comorbid LS and indicates a need for clinicopathologic correlation. Pathologists must clearly communicate a finding of LS, as clinicians focused on surveillance of HSIL may not otherwise recognize the comorbid diagnosis and attendant dVIN risk. The novel finding that LS-related sclerosis may disappear under HSIL leads to a hypothesis that collagen abnormalities are driven by epithelial behavior. Epitopic expression of basal cells in HSIL would be different to LS-affected epithelium, and this may alter T-cell–mediated attack and remove the impetus for hyalinization or fibrosis.

There is robust evidence that dVIN has higher rates of concurrent and subsequent SCC than HSIL; excision with clear margins is the mainstay of dVIN management.[1,24] In contrast, rates of HSIL progression are lower and disease may spontaneously regress, allowing for consideration of excision, LASER, imiquimod, or close observation in well-selected cases. In this cohort, clinicians elected a multimodal approach in 28%. The use of imiquimod in women with LS/LP is limited by irritative effects and unknown efficacy in a field of local immunosuppression.[6] Rarely, imiquimod may provoke a lichenoid drug reaction seen as de novo LS at the application site, further complicating assessment.[25] Whole LGT surveillance is advised for uVIN because the rate of concurrent or subsequent cervical, vaginal, and/or anal disease is 4%–20%; international guidelines offer few specifics about how to accomplish this, so practice varies across hospitals and regions.[26–30] The adjunctive role of HPV vaccination in older women treated for LGT HSIL has not been investigated, but recurrence risk reduction has been demonstrated in women younger than 45 years treated for cervical disease.[31] Controversy also persists regarding surveillance schedules and optimal steroid maintenance regimens for LS/LP.[32,33] The impact of topical corticosteroids on emergence of HSIL is poorly understood, but a restrictive approach to LS/LP treatment may increase risks of scarring and HPV-independent neoplasia.[5,6,8,32] Given these issues and the relative rarity of comorbid HSIL and LS/LP, an expert multidisciplinary approach may improve case ascertainment and allow for development of a standard approach to treatment and surveillance within an institution or health system.

Limitations of the study are those inherent to a single-site retrospective design, to include incomplete records, clinical variation, ascertainment bias, and nonuniversal clinical photography. The number and characteristics of LS/LP-affected women without HSIL are unavailable because the local pathology department accepts specimens from multiple private and public practices across 2 states. Discussions around HPV vaccination were infrequently documented, so it is impossible to comment on the impact of previous or peritreatment vaccination. Cases of separate location were likely underrepresented, because inclusion required clinicians to recognize the skin abnormality, obtain a separate biopsy, and have that specimen be diagnostic of LS or LP. In contrast, women with co-located disease might have LS or LP verified each time they undergo an excision of HSIL.

CONCLUSIONS

Comorbid vulvar HSIL and LS/LP may be overlapping, adjacent, or separate and is associated with high rates of tobacco use, immunologic dysfunction, and HPV-independent neoplasia. Although it is essential for the pathologist to distinguish between HPV-related and HPV-independent disease, challenges include the frequency of keratinizing morphology and the variable appearance when HSIL overlies LS. Clinicopathologic correlation, p16, and p53 are essential tools to arrive at the best diagnosis. Although there is scant literature to inform treatment, surveillance, and prognosis in this high-risk group of women, management plans should involve frequent specialist visits, control of the dermatosis, a low threshold for biopsy and excision, and expert multidisciplinary review before ablative or extirpative procedures.

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