Vaginal Intraepithelial Neoplasia: Histopathological Upgrading of Lesions and Evidence of Occult Vaginal Cancer

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Objective: The aim of this study was to analyze women treated with excisional procedures for vaginal high-grade squamous intraepithelial lesions (HSILs). The histopathological upgrading of the lesions previously detected on vaginal biopsy and the presence of occult invasive vaginal cancer in the specimens excised were investigated, to identify a higher risk subset of women.

Materials and Methods: A retrospective analysis of the medical records of 86 women with a biopsy histopathologic diagnosis of vaginal HSIL (vaginal intraepithelial neoplasias [VaINs]: VaIN2 and VaIN3) and subsequent excisional therapy, consecutively referred to the Aviano National Cancer Institute (Aviano, Italy) from January 1991 to April 2014, was performed.

Results: Of the 86 patients, 4 cases (4.6%) of occult vaginal cancer were detected, all of them in women previously diagnosed with VaIN3 on biopsy (4/39 cases, 10.3%). Women with diagnosis of VaIN2 on biopsy showed an upgrading of lesions, with diagnosis of VaIN3 on the final specimen in 5 (10.6%) of 47 cases, with no cases of VAIN2 upgraded to invasive cancer. In 33.3% of the women initially diagnosed with VaIN2 and with previous hysterectomy for human papillomavirus–related disease, a final histopathological upgrading of lesions emerged. Furthermore, tobacco use was significantly related to the histopathological upgrading of lesions previously detected on vaginal biopsy.

Conclusions: Women diagnosed with VaIN3 should be treated with excisional procedures as first-line surgical approach, given the risk of occult invasive disease in 10% of the cases. Women diagnosed with VaIN2 and with previous hysterectomy for human papillomavirus–related cervical diseases should always be carefully evaluated and possibly excised, given the higher risk of histopathological upgrading of lesions and thus the potential risk of occult vaginal cancer. Tobacco users should be considered as high-risk group.

Key Words: high-grade vaginal intraepithelial neoplasia, VaIN, vaginal cancer, occult cancer, histopathological upgrading

Vaginal intraepithelial neoplasia (VaIN) is a rare human papillomavirus (HPV)–related intraepithelial lesion of the female lower genital tract[1] with an estimated incidence from 0.2 to 2 per 100,000 women per year.[2] The natural history of VaIN is not completely known, including progression toward invasive squamous cell vaginal cancer.[1,3–6] In the mid 1980s, VaIN was subclassified in VaIN1 (mild dysplasia), VaIN2 (moderate dysplasia), and VaIN3 (severe dysplasia/carcinoma in situ [CIS]). VaIN1 can be considered as the transient expression of HPV infection, with a high rate of spontaneous regression,[6,7] and is now defined as "low-grade VaIN" (LG-VaIN) or vaginal LSIL. VaIN3 is now defined as "high-grade VaIN" (HG-VaIN)[1,7–10] or "vaginal HSIL" according to the 2012 revised Lower Anogenital Squamous Terminology Standardization (LAST) terminology[10] because of its potential progression toward vaginal cancer. The VaIN2 category is not a reproducible histopathologic category among pathologists[10–12] and the risk of progression for lesions classified as VaIN2 is intermediate between VaIN1 and VaIN3.[10] Cases documenting vaginal HSIL can also harbor occult invasive lesions, and previous published data reported a 12% incidence of invasive vaginal cancer in histopathological specimens of women excised for VaIN2 and VaIN3,[13] whereas up to 28% of occult invasive disease was found in women excised for VaIN3.[12]

Because of the lack of complete knowledge of the natural history of VaIN, the optimal management of vaginal HSIL remains a "therapeutic dilemma."[11] However, excisional treatments are considered the treatment of choice, especially if occult invasion cannot be excluded.[14] Surgical excisions of vaginal lesions are more difficult to perform than ablative treatments and burdened by a higher rate of complications that may involve adjacent pelvic organs.[13,15] Thus, the choice of an excisional treatment is justified only by the need to identify invasive lesions to treat them adequately.[11]

The aim of this study was to analyze the women treated with excisional procedures for vaginal HSIL, evaluating the rate of histopathological upgrading of the lesions previously detected on vaginal biopsy and otherwise occult invasive vaginal cancer, to identify a higher risk subset of women.

MATERIALS AND METHODS

All women with a histopathological diagnosis of VaIN2 or VaIN3, consecutively referred to the Gynecological Oncology Unit of the Aviano National Cancer Institute (Aviano, Italy) from January 1991 to April 2014, were considered.

These women were diagnosed with vaginal HSIL after biopsy of suspicious areas detected by colposcopy after abnormal cytology. Colposcopic examinations were recorded according to the 2012 revised colposcopic terminology of College of American Pathologists and the American Society for Colposcopy and Cervical Pathology (LAST).[10] The colposcopies performed before the introduction of the 2012 LAST terminology were revised accordingly.

All the colposcopies and the vaginal biopsies were performed by the same gynecologic oncologists of our institute (F.S. and G.D.P.), with particular expertise in the management of preinvasive and invasive lesions of the lower female genital tract. Similarly, all the subsequent histopathological evaluations of the specimens collected were performed by the same pathologist of

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our institute (V.C.), with particular expertise in gynecologic-oncologic disease.

All the women considered were diagnosed with vaginal HSIL for the first time; women with previous diagnosis and treatments for vaginal HSIL were excluded. Women with a previous diagnosis of vaginal HSIL and 1 or more therapies at other institutions were excluded to avoid potential confounding factors. Indeed, the disease may have been treated in centers with different therapeutic standards and the disease recurrence could be both a sign of increased aggressiveness of the VaIN or inadequate previous treatments. Women with synchronous high-grade cervical intraepithelial lesions (CINs 2/3) or cervical invasive cancers detected at the time of the colposcopic examination were also excluded.

Patients were identified by searching our clinical databases, and the medical records of women fulfilling the study inclusion criteria were retrospectively analyzed in a retrospective case series. Data obtained included information regarding pertinent medical and surgical history and sociodemographic characteristics of each woman.

Among the women diagnosed with vaginal HSIL and fulfilling the study inclusion/exclusion criteria, only those who subsequently underwent a surgical excisional treatment at our institute were included in the present analysis. The excisional procedures performed were CO_2-laser excision or CO_2-laser skinning colpectomy, radio-frequency excision, or cold-knife upper colpectomy (with vaginal or abdominal access).

Statistical analysis was performed using IBM SPSS Version 22.0 (IBM Corporation, Armonk, NY). χ^2 testing and Fisher exact test were used, as appropriate, to evaluate associations. A p value of less than .05 was considered as statistically significant. Multivariable logistic regression was performed to adjust for potential confounding variables.

Institutional internal review board approval (Centro di Riferimento Oncologico, Aviano, Italy IRB Number 17/2013) was obtained.

RESULTS

From January 1991 to April 2014, a total of 175 women referred to the Gynecological Oncology Unit of the Aviano National Cancer Institute (Aviano, Italy) were diagnosed with vaginal HSIL (VaIN2/VaIN3) for the first time. The mean (SD, range) age of these women was 45.3 (13.8, 8–78) years.

Two women showed synchronous cervical invasive cancer, whereas in 2 cases, the histopathological data were not completely available in the medical charts; thus, these 6 women were excluded.

Among the remaining 169 women, 83 underwent ablative procedures (CO_2-laser vaporization) after the biopsy histopathological diagnosis of vaginal HSIL and were not included in the present analysis.

The remaining 86 women were treated with excisional procedures as first-line surgical therapy and constituted the case series for this report. Eighty women underwent CO_2-laser excision of the vaginal walls or CO_2-laser skinning colpectomy of the vaginal vault, 1 patient underwent a radio-frequency excision, and 5 women underwent a cold-knife upper colpectomy. For all of these women, a specimen suitable for a complete histopathological evaluation was obtained.

No significant differences in women treated by excision versus those treated by ablative methods were found (mean [SD] age: 47.5 [13.5] vs 44.3 [15] years, p = .15; tobacco use: 24.4% vs 24.1%, p = .9; menopause: 54.6% vs 42.2%, p = .14; previous diagnosis of HPV-related cervical disease: 50% vs 47%, p = .81; previous hysterectomy: 38.4% vs 30.1%, p = .33; previous hysterectomy for CIN/CIS/cervical cancer: 27.9% vs 19.3%, p = .26; unifocal lesion: 44.2% vs 28.9%, p = .06).

Women who have undergone excisions were more likely to have HSIL (VaIN3) on biopsy (45.3% vs 26.5%; p = .02).

The histopathological characteristics of the study group are reported in Table 1.

The mean (SD, range) age in the study group was 47.5 (13.5, 25–78) years and 47 women (54.6%) were in postmenopausal status. Tobacco use was reported in 21 women (24.4%) and HIV infection was present in 2 cases (2.3%). Previous diagnosis of HPV-related cervical disease (CIN, CIS, or invasive cancer) was reported in 43 cases (50%). Thirty-three women (38.4%) had hysterectomy before the initial diagnosis of vaginal HSIL; hysterectomy was performed because of CIN/CIS or invasive cervical cancer in 24 cases. In the remaining 9 cases, hysterectomy was performed for benign conditions and no previous HPV-related disease of the lower genital tract had been reported in these women.

In 47 cases (54.7%), the initial histopathological diagnosis on vaginal colposcopy-guided biopsy was VaIN2; 39 cases (45.3%) were diagnosed with VaIN3.

Final histopathological evaluation after the excisional treatment resulted in upgrading of lesions in 9 cases of vaginal HSIL excised (10.5%); 4 cases (4.6%) of occult invasive vaginal cancer were detected.

The clinical and histopathological characteristics of the 4 patients with occult vaginal cancer are reported in Table 2.

For women with initial biopsy histopathologic diagnosis of VaIN2, the final diagnosis on the specimen excised with surgery was ≤ VaIN2 in 42 cases (89.4%); a histopathological upgrading of lesions (≥VaIN3 on the final specimen) was diagnosed in 5 cases (10.6%). No occult invasive vaginal cancer was detected in this group.

For women with initial biopsy histopathologic diagnosis of VaIN3, the final diagnosis on the specimen excised with surgery was ≤ VaIN3 in 35 cases (89.7%); 4 (10.3%) of the 39 women were diagnosed with occult invasive vaginal cancer on the final specimen.

In the whole study group, 33 women had a previous hysterectomy before the diagnosis of vaginal HSIL. In these patients, 1 case (3.0%) of occult invasive disease was reported, whereas the other 3 cases of occult vaginal cancers were detected in the remaining 53 woman without previous hysterectomy (5.7%). The rate of detection of occult vaginal invasive disease was similar in the 2 groups (3.0% vs 5.7%, p = .96).

Considering only the 24 women who previously underwent hysterectomy for CIN/CIS or cervical cancer, 1 case of occult vaginal invasive cancer was identified in the specimen excised after

TABLE 1. Histopathological Characteristics of the Study Group (N = 86)

	VaIN2 on biopsy (n = 47)	VaIN3 on biopsy (n = 39)
Excisional procedures performed, n (%)		
CO_2-Laser excision/skinning colpectomy	47 (100)	33 (84.6)
Radio-frequency excision	—	1 (2.6)
Upper colpectomy	—	5 (12.8)
Histology on specimen excised, n (%)		
Negative/VaIN1	22 (46.8)	4 (10.3)
VaIN2	20 (42.6)	8 (20.5)
VaIN3	5 (10.6)	23 (58.9)
Invasive carcinoma	—	4 (10.3)

TABLE 2. Clinical and Histopathological Characteristics of Women With Occult Invasive Vaginal Cancer on Excision

	VaIN	Age, y	Menopause	Previous hysterectomy	Previous diagnosis of cervical HPV-related disease	Tobacco use	Localization and no. lesions	Colposcopic appearance	Depth of invasion on excision, mm
1	VaIN3	42	Yes	Yes (CIN3/CIS)	Yes (CIN)	Yes	Upper third (single lesion)	Thin acetowhite epithelium, with regular punctuation, iodine negative	<1
2	VaIN3	56	Yes	No	Yes (CIN)	No	Upper third (4 lesions)	Thin acetowhite epithelium, iodine negative	<1
3	VaIN3	58	Yes	No	No	Yes	Upper third (single lesion)	Thin acetowhite epithelium, iodine negative	<1
4	VaIN3	26	Yes	No	No	Yes	Upper third (3 lesions)	Thin acetowhite epithelium, with coarse punctuation, iodine negative	4

the diagnosis of vaginal HSIL (4.2%). In the remaining 62 women, the rate of occult invasive cancer detected was 4.8%. The rate of detection of occult vaginal invasive disease was comparable in the 2 groups (4.2% vs 4.8%, $p = .65$).

Of the 47 women initially diagnosed with VaIN2 on biopsy, a previous hysterectomy for cervical HPV-related disease (CIN, CIS, or invasive cervical carcinoma) had occurred in 9 cases. No occult invasive vaginal disease was reported in these 9 women, but a histopathological upgrading of lesions, with detection of VaIN3 on the specimen excised, was found in 3 (33.3%) of the 9 cases. Of the 38 women initially diagnosed with VaIN2, without a previous hysterectomy for cervical HPV-related disease, only 2 cases (5.3%) of histopathological upgrading of lesions, with detection of VaIN3 on the specimen excised, were reported. This difference was not statistically significant (33.3% vs 5.3%, $p = .06$).

Of the 39 women initially diagnosed with VaIN3 on biopsy, a previous hysterectomy for cervical HPV-related disease (CIN, CIS, or invasive cervical carcinoma) was reported in 15 cases. One case of occult invasive vaginal cancer was detected in the specimen excised after the initial diagnosis of VaIN3 in these 15 women (6.7%). In the 24 women initially diagnosed with VaIN3, without a previous hysterectomy for cervical HPV-related disease, 3 cases (12.5%) of occult vaginal invasive cancers were detected on the specimens excised. No significant difference was identified (6.7% vs 12.5%, $p = .97$).

The multivariable logistic regression analysis of potential risk factors related to the histopathological upgrading of vaginal lesions did not show significant differences with respect to HIV infection ($p = .24$), menopausal status ($p = .14$), previous diagnosis of HPV-related disease ($p = .58$), previous hysterectomy ($p = .99$), or grade of VaIN diagnosed on the biopsy ($p = .81$; see Table 3). Notably, tobacco was significantly related to the histopathological upgrading of lesions previously detected on vaginal biopsy ($p = 0.01$).

DISCUSSION

Although the true prevalence of VaIN is unknown, the incidence of this condition has increased steadily over the recent years because of the widespread use of screening methods. However, VaIN remains a rare condition and with a lack of a complete knowledge of its natural history, the optimal management of vaginal HSIL actually remains a therapeutic dilemma.[11]

Several therapeutic strategies have been proposed to treat vaginal HSIL, primarily distinguished between excisional procedures and ablative therapies. Surgical excision procedures have the advantage to provide a tissue specimen suitable for a complete histopathological evaluation, with the possibility to identify underlying cancer. However, the typical upper vaginal location of vaginal HSIL,[4–6] especially in hysterectomized women, could make excisional procedures very difficult to perform.

For multifocal lesions involving the upper third of the vagina, the traditional cold-knife partial vaginectomy has been proposed as the elective excisional procedure,[4,13] but disadvantages include risk of hemorrhage, injury to the bladder or rectum, and vaginal shortening or stenosis[13]; in different studies, the cure rate after a upper vaginectomy varied from 68% to 88%.[3,12,13] Carbon dioxide–laser excision of the vaginal walls or CO_2-laser skinning colpectomy of the vaginal vault has been used to treat vaginal HSIL with excellent results.[11] These techniques, if performed by expert surgeons, are associated with low rate of complications, and a tissue specimen suitable for a complete histopathological evaluation can be obtained. Carbon dioxide–laser excisions, however, are technically more difficult to perform than ablative procedures; they should be properly considered as first-line surgical therapy only in women at risk for occult invasive vaginal cancer.

Ablative procedures are more feasible techniques, with low complications rates in most of the cases. Carbon dioxide–laser

TABLE 3. Multivariable Logistic Regression of Risk Factors for Histopathological Upgrading of the Lesions Previously Detected on Vaginal Biopsy

	Upgraded (9 cases), n (%)	Not upgraded (77 cases), n (%)	Adjusted odds ratio (95% CI)	*p*
Tobacco use	6 (66.6)	15 (19.5)	7.8 (1.55–39.05)	.01
HIV infection	1 (11.1)	1 (1.3)	8.23 (0.24–277.5)	.24
Menopause	7 (77.7)	40 (51.9)	0.2 (0.02–1.68)	.14
Previous diagnosis of HPV-related cervical disease	5 (55.5)	38 (49.3)	1.98 (0.16–23. 93)	.58
Previous hysterectomy	4 (44.4)	29 (37.6)	—	.99
Previous hysterectomy for CIN/CIS/ cervical cancer	4 (44.4)	20 (25.6)	—	.99
VaIN3 on biopsy	4 (44.4)	35 (45.4)	1.21 (0.23–6.30)	.81

vaporization is the most commonly used ablative procedure, with a cure rate from 50% to 100%.[13,16] The main advantage is the possibility to control exactly the depth and width of destruction, and a rapid posttreatment healing is reported.[17] Moreover, it can be performed as an outpatient procedure and it is suitable for multifocal lesions.[4] Recently, Perrotta et al.[16] have proposed CO_2-laser vaporization for the initial treatment of vaginal HSIL, reporting a cure rate of 86% (95% CI = 63.7%–97%). However, the small sample size (21 patients) and the short median follow-up (25 months) limited the applicability of these results.

Ablative therapies have some limitations: the lesion should be fully visible and, most importantly, should be adequately assessed by biopsies to exclude invasion. Where invasion is suspected or cannot be excluded (e.g., in lesions at the vault suture line after hysterectomy), surgical excision should be preferred.[14]

However, given the higher rate of complications of excisional procedures, including risk of hemorrhage and injury to the bladder or rectum, the most appropriate therapy should be tailored for each patient and, for example, in elderly women with notable vaginal dystrophy, in women in which topical estrogen therapy is contraindicated, or in patients with comorbidities, sometimes, we opted for the more feasible ablative procedures.

Unfortunately, because of the retrospective nature of this study, it was not possible to identify the factors that influenced the choice of treatment modality in all the 175 patients initially referred to our institution during the study period.

The potential progression of vaginal HSIL toward invasive cancer and the risk of occult vaginal invasive disease have to be considered in the choice of an appropriate surgical treatment for these women.

The most appropriate therapeutic approach of vaginal HSIL and, in particular, the potential cure rate of ablative procedures are currently under debate,[16] and further studies addressing this important issue are needed. However, in this study, we did not want to analyze the efficacy of excisions or ablations in the therapy of vaginal HSIL. The aim of this study was to analyze only the women treated with excisional procedures, evaluating the histopathological upgrading of the lesions previously detected on vaginal biopsy and the risk of occult invasive vaginal cancer in the specimens excised, to identify a higher risk subset of women.

The classification into LG-VaIN and HG-VaIN is currently in evolution, and in particular, the real potential of progression toward invasive vaginal cancer of VaIN2 is discussed.[2–11] Indeed, among vaginal HSIL, only VaIN3 is currently considered as the true precursor of vaginal cancer, because a higher rate of occult superficially invasive vaginal cancer is reported in women with these lesions.[10,11]

In our case series, 93% of the women who underwent excisional procedures were treated with CO_2-laser excision of the vaginal walls or CO_2-laser skinning colpectomy and no case of complication was reported. All the specimens excised were suitable for a complete histopathological evaluation, with detection of occult invasive cancer in 4 cases, and the surgical margins were negative for epithelial dysplasia or invasive cancer in all the cases. All of the occult invasive cancers were detected in women with a previous biopsy of VaIN3 (4/39 cases, 10.3%).

No case of occult invasive disease was detected in women excised for VaIN2. This finding could be due to the accuracy of diagnostic process, with adequate biopsy of vaginal lesions and correct definition of the grade of dysplasia, but also to the natural history of VaIN2 with a slow progression toward VaIN3 and invasive cancer. The VaIN2 category is not always a reproducible histopathologic category among pathologists,[10–12] and probably, the presence of VaIN3 is an expression of a biologically more aggressive disease related to a persistent high-risk HPV infection. However, further studies analyzing the natural history of VaIN2 and its trend of progressions toward invasive cancers are needed.

In women with a biopsy histopathologic diagnosis of VaIN2, a histopathological upgrading of lesions (with diagnosis of VaIN3 on the final specimen) was detected in 10.6% of the cases. Considering only those women diagnosed with VaIN2 and with previous hysterectomy for CIN/CIS or cervical cancer, the rate of histopatological upgrading of lesions (with diagnosis of VaIN3 on the final specimen) was 33.3%. In these cases of histopathological upgrading of lesions, the pathologist had reassessed the previous biopsy to confirm the discrepancy with the final examination. In all cases, the patients underwent excision of the lesion within 60 days after the biopsy diagnosis of vaginal HSIL. Therefore, we believe that it is unlikely that this discrepancy could be explained by the interval of time between the biopsy and the excision.

According to our results, tobacco use seems to be a further risk factor for histopathological upgrading of VaIN. Many studies confirmed the role of tobacco use as an important risk factor for the development of high-grade cervical intraepithelial neoplasia and cervical cancer.[18,19] Sherman et al.[20] reported a similar risk also for the development of vaginal HSIL; however, no study analyzed the role of tobacco in the risk of histopathological upgrading of vaginal intraepithelial lesions previously detected on biopsy. Similarly to the increased risk of progression of CIN to cervical cancer among smokers, tobacco users should be considered as high-risk group and thus they should undergo excisional procedures because an ablative procedure may not allow detection of all the patients requiring further treatments in case of diagnosis of vaginal cancer.

A previous hysterectomy for HPV-related cervical invasive or preinvasive lesions is believed to be associated with the development of vaginal HSIL,[5] and often, the biopsy diagnosis of VaIN in hysterectomized women is technically difficult, given the redundancy of the vaginal mucosa, and at times lesions may be obscured by the cuff.[1] Thus, even if in the present study, no significantly higher risk of occult invasive disease in hysterectomized women emerged, these patients should be always carefully evaluated.

This retrospective case series included a large number of vaginal HSIL cases. Moreover, all the colposcopies and vaginal biopsies and the subsequent histopathological evaluations were performed in a single institution, by the same gynecologists (F.S. and G.D.P) and the same pathologist (V.C.) of the Aviano National Cancer Institute, with particular expertise in gynecologic-oncologic disease.

To our knowledge, no previous studies analyzed the histopathological upgrading of vaginal intraepithelial lesions previously detected on biopsy, and only few studies analyzed the rate of occult invasive cancers detected in specimen of the women excised for vaginal HSIL.[12,13] Moreover, some previous studies on VaIN included a relatively small number of patients[16] or considered LG-VaIN and HG-VaIN together.[1]

The LAST project affirmed that if the pathologist is entertaining an hematoxylin and eosin stain morphologic interpretation of –IN 2 (under the old terminology, which is a biologically equivocal lesion falling between the morphologic changes of HPV infection and precancer), p16 imunohistochemical staining is recommended to help clarify the situation. However, the p16 imunohistochemical expression in women diagnosed with VaIN2 was not routinely performed in our institution until 2013. Thus, the p16 confirmation was available only for 5 cases of VaIN2 (all of them with strong and diffuse block-positive p16 results). This could be considered as a potential limitation of our study.

CONCLUSIONS

Treatment options for vaginal HSIL should be tailored individually, given the disease distribution, the biopsy histopathology of VaIN, the presence of particular risk factors, and the prognosis of recurrence of the vaginal lesions.

In our opinion, women diagnosed with VaIN3 should be treated with excisional procedures as first-line surgical approach, given the risk of occult invasive disease in the 10% of the cases. Even the women diagnosed with VaIN2 with previous hysterectomy for HPV-related cervical diseases should be excised, given the higher risk of histopathological upgrading of lesions and thus the potential risk of occult vaginal cancer. Tobacco users should be considered as high-risk group, and thus, they should undergo excisional procedures. Given the potential technical difficulties, these excisional procedures should be performed by expert gynecologists.

The data of this study could be useful for clinicians to provide an appropriate counseling to women diagnosed with vaginal HSIL, to propose the appropriate management.

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