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Prevalence of vulvar intraepithelial neoplasia: Experience in a tertiary Government Hospital

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Abstract:

Vulvar intraepithelial neoplasia (VIN) is a precancerous lesion involving the squamous epithelium of the vulva. This retrospective descriptive study aims to determine the prevalence of VIN in a tertiary government hospital in a developing country. Medical records of outpatient consultations with the diagnosis of VIN from January 2000 to June 2012 were reviewed. The prevalence of VIN was 1.6/100,000 women over the 12 years. The diagnosis was based on biopsy results of an incidental finding of vulvar lesions on physical examination. The profile of a patient with VIN was a woman aged 40 years old and above, married, multigravid, nonsmoker, high school graduate, and unemployed. Vulvar lesions noted were multiple hyperpigmented papules located at the posterior labia majora. VIN was associated with abnormal colposcopy findings, and 40% were associated with concomitant cervical disease. Treatment was wide local excision. Prompt diagnosis and appropriate treatment of VIN aim to prevent its progression to vulvar carcinoma. Although vulvar carcinoma is a rare condition, there has been a notable rise in prevalence in recent years. Hence, gynecologists should be vigilant and have a high index of suspicion to detect the disease early in its course.

Keywords:

Premalignant, vulvar disease, vulvar intraepithelial neoplasia, vulvar lesions

Introduction

Vulvar intraepithelial neoplasia (VIN) is a precancerous lesion involving the proliferation of atypical basal cells in the squamous epithelium of the vulva that may lead to invasive vulvar carcinoma if left untreated.[1,2]

Although vulvar carcinoma is a rare condition, an evolving disease spectrum must be recognized since its incidence has been observed to rise over the past few decades, particularly in younger women.[2-4] An annual incidence rate of 1.2/100,000 women has been reported; with an increasing incidence of 2.86/100,000 women per year.[4]

Unfortunately, no screening programs exist. The identification of such lesions relies heavily on clinical suspicion and a thorough examination of the vulva. It is, therefore, essential that the gynecologist should be aware of the classification and descriptions of these lesions for accurate identification.

Nelson *et al*. reported more than a four-fold increase in VIN in the past 30 years,[1,3,4] becoming more frequent in young women between 20 and 35 years of age.[5] Studies by Jones and Rowan and Joura also revealed increasing incidences of VIN-related invasive vulvar cancer in the young.[6,7] Locally, there has been no established data on the incidence or prevalence of VIN.

Historically, various terms have been used to define VIN. In 1986, the International Society for Vulvovaginal Disease (ISSVD) adopted the single term VIN, discouraging

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any other terminology including carcinoma *in situ* and vulvar atypia. The term VIN included three subdivisions: VIN 1 (mild dysplasia), VIN 2 (moderate dysplasia), and VIN 3 (severe dysplasia), equivalent to the classification of cervical intraepithelial neoplasia (CIN), although there is no evidence that the morphologic spectrum of VIN 1–3 reflects a biologic continuum or that VIN behaves similarly to CIN. Hence, this classification created a lot of controversy and confusion.[1,2,4] In 2004, ISSVD modified the VIN terminology, this time into a two-tier classification: uVIN, classical or usual type (warty, basaloid, and mixed) and dVIN, differentiated type. The two types differ in morphology, biology, and clinical features. In this most recent classification, the term VIN 1 is no longer applied. VIN should apply only to histologically "high-grade" squamous lesions. Therefore, it is recommended that the former terms VIN 2 and 3 are combined as a single diagnostic category, and referred to as high-grade VIN, usual, or differentiated type.[1,3,8,9] In 2015, ISSVD once again changed the terminology of VIN to unify the nomenclature of human papillomavirus (HPV)-associated squamous lesions of the lower genital tract. The ISSVD recommends the terms low-grade squamous intraepithelial lesion of the vulva (vulvar LSIL) and high-grade squamous intraepithelial lesion of the vulva (vulvar HSIL) for histopathologic diagnosis of productive HPV infections, which includes external genital warts and precancer, respectively. Based on the current classification, the usual type VIN is now classified as vulvar HSIL and differentiated VIN remains. Flat lesions with basal atypia and koilocytic changes which were previously termed VIN 1 are now considered vulvar LSIL (condyloma or HPV effect).[10]

Sixty percent of women with VIN present with vulvar pruritus; however, many can be asymptomatic with a lesion incidentally noted on routine examination. Other symptoms include vulvar itching, burning, pain, and dyspareunia. Lesions noted upon examination have no single pathognomonic feature to point to a definite diagnosis of VIN. They are variable in appearance and color, ranging from white, red, and brown to gray. However, elevated, white, irregular lesions may confer the highest risk for VIN.[4] Over 80% of VIN-affected women present with multifocal vulvar disease, and often neoplastic changes can be found in the entire lower genital tract. Clinically, it is important to distinguish unifocal from multifocal lesions, since unifocal VIN tends to progress to invasive carcinoma ten times more often than multifocal VIN.[1]

Usual VIN or vulvar HSIL (uVIN) occurs predominantly in younger women with the highest incidence at 45–49 years old. It is linked to HPV infection, most often HPV 16, and less commonly HPV 18 or HPV 33, therefore, risk factors include those related to the acquisition of HPV infection: multiple sexual partners, impaired immunologic status, smoking, and age of first coitus.[8] Other factors associated with increased risk for VIN include poor education, the presence of other genital infections, and infrequent pelvic examinations, although epidemiologic evidence is still lacking.[1] These lesions present as a multifocal and multicentric disease associated with other lower anogenital intraepithelial neoplasia and have the potential to progress to invasive carcinoma. It is localized in the mucosa and nonhairy areas, mostly in the lower third of the vulva. It is seen adjacent to approximately 30% of squamous cell carcinomas of the vulva.[1,4,8,9] Differential diagnoses for uVIN include reactive epithelial changes, vulva Paget's disease, and malignant melanoma.[8]

On the other hand, VIN differentiated type (dVIN) affects older women, usually in postmenopausal women with a mean age of 68 years.[8] It is not related to HPV and is associated with vulvar dermatosis, particularly lichen sclerosus[8,9] as well as keratinizing squamous cell carcinoma. Unlike uVIN, dVIN presents symptomatically, most often with a long history of itching. Lesions are unifocal and unicentric, white-keratotic or red, and localized in hairy areas.[1] Differential diagnoses for dVIN include benign processes with acanthosis and focal nuclear atypia, pseudoepitheliomatous hyperplasia, and inflammatory dermatologic lesions.[8]

VIN is a histopathological diagnosis confirmed by pathologists with expertise in gynecology.[11] In general, VIN is described by loss of epithelial cell maturation – abnormal mitotic figures, nuclear hyperchromasia, and cellular crowding. VIN can be subclassified into the histologic subtypes warty or basaloid (uVIN of vulvar HSIL) and differentiated (dVIN) based on morphologic criteria. Histological changes seen in uVIN are associated with the integration of high-risk oncogenic HPV infection into the host genome.[8] The epidermis is thickened with parakeratosis and hyperkeratosis. Abnormal cell maturation is characterized by multinucleation and abnormal mitotic figures. Warty uVIN has rete ridges that are wide and deep, often reaching close to the surface. Aside from the marked papillary pattern, warty uVIN is characterized by acanthosis and prominent koilocytic changes.[4,5,8,9] Conversely, basaloid VIN is characterized by a flat lesion composed of small uniform cells which resemble basal cells with high nuclear to cytoplasmic ratios and minimal koilocytic changes replacing the full thickness of the epidermis. There is frequent overlap between the two patterns with some VIN cases showing features from both types. This suggests that they may belong to a spectrum of a single disease.[8] Léonard *et al*. mentioned a rare variant called "pagetoid VIN" where atypical squamous cells present a pale cytoplasm and are

isolated or grouped in small clusters.[9] With the benefit of immunohistochemistry, uVIN lesions are showed to have a strong, nuclear-cytoplasmic band-like pattern of staining with p16, and increased proliferative activity with Ki-67 where positive cells extend into the upper two-thirds of the epithelial thickness.[8] Alternatively, the histologic changes in dVIN are subtler and not easily recognized from benign dermatosis. dVIN is described by a thickened parakeratotic epithelium with elongation and anastomosing rete ridges. A notable feature is the presence of squamous cells with abundant bright eosinophilic cytoplasm and typically prominent intercellular bridges. These keratinocytes are present in the basal and mid-layers of the epithelium with evident cytological abnormalities. Mitotic activity is common in the base of the epidermis and no koilocytic changes are identified.[8,9]

Although spontaneous regression may occur, treatment is warranted for women with VIN because of the invasive potential of this disease (5.7% for uVIN and 30% for dVIN).[8,10] Although conservative measures have been gaining popularity, surgery remains as the first line of treatment for VIN.[3] Wide local excision is the initial intervention for women in whom clinical or pathological findings suggest invasive cancer.[4,5,8-10] In one study, 4% of patients initially diagnosed from the biopsy with VIN 3 were found to have microinvasive disease after definitive excision.[12] Microscopic disease may extend further than the visible acetowhitening used to guide surgical excision, thus a margin of normal tissue should be excised in addition to the lesion. Clinical practice guidelines from the Society of Gynecologic Oncologists recommend local excision of all gross diseases with a 0.5- to 1-cm margin of normal tissue.[4,12] Skinning vulvectomy where all the vulvar skin is removed is rarely necessary, although it may be useful for cases of confluent multifocal lesions that may be seen in immunocompromised women.[11] CO_2 laser ablation is usually used in cases where cancer is not highly suspected. It can be used for single, multifocal, or confluent lesions, although the risk for recurrence may be higher than with excision.[3,4,9] As with excision, there should be a disease-free margin. In contrast to laser ablation of genital warts, laser application for VIN entails the destruction of cells through the full thickness of the epithelium. Since surgery can be disfiguring, especially in cases with multifocal disease, great interest has been paid to nonsurgical management of VIN,[3] the most promising being imiquimod application. According to American College of Obstetricians and Gynecologists (ACOG), randomized control trials have shown that the application of topical 5% imiquimod is effective, although it is not approved by the US Food and Drug Administration. The regimen mentioned in the studies includes three times weekly application to the affected areas for 12–20 weeks along with colposcopic assessment at 4–6-week intervals during treatment. Residual lesions would still require surgical treatment.[10]

Objective

The objective of this study was to determine the prevalence of VIN among women consulting for gynecologic concerns over 12 years in a tertiary government hospital.

Materials and Methods

This retrospective descriptive study was approved by the Ethics Review Board. Outpatient gynecologic consultations from January 2000 to June 2012 were reviewed, and medical records of patients with physical findings suggestive of VIN were retrieved. Patients with histopathologic reports confirming the diagnosis of VIN were included in the study. Demographic data, description of the lesion, pap smear results, colposcopy findings, and treatment were collected. Descriptive statistical analysis was used, and data were expressed as frequency, percentage, mean standard deviation, and range.

Results

From 2000 to 2012, a total of 305,964 gynecologic consultations were reported, out of which nine[9] patients had a diagnosis of rule out VIN. Five cases[5] were confirmed by histopathology as VIN. The prevalence of VIN in this study was 1.6/100,000 over 12 years [Table 1].

For clinical presentation, one consulted for an abnormal pap smear, while one case each had vulvar pruritus, vaginal discharge, or postcoital bleeding. Only one case sought to consult for a mass at the labia majora [Table 2]. The first coitus occurred during their early 20s with one sexual partner. All cases had their first delivery in their early 20s. For contraception, two (40%) used oral contraceptive pills, one (20%) used depot medroxyprogesterone acetate, and two did not use any form of contraception. Four (80%) finished high school, while one had elementary education. Only one patient worked as a house helper, while the rest were unemployed. Three patients (60%) were nonsmokers but exposed to secondhand smoke.

Table 3 summarizes physical findings and comorbidities. Bilateral involvement of the labia majora was noted in two cases (40%) and was located either inferiorly or superiorly. Gross inspection revealed hyperpigmented lesions in four cases (80%) while one presented with an erythematous papule. Lesions were nodular in two cases (40%). Three cases had comorbid gynecologic conditions. Two had CIN while another patient had cervical adenocarcinoma, stage IB1.

Table 1: Sociodemographic profile and risk factors of patients diagnosed with vulvar intraepithelial neoplasia at a Tertiary Government Hospital from 2000 to 2012

Patient number	Age at diagnosis	Civil status	Education	Occupation	Smoking	Alcohol drinking	Contraceptive use
1	44	Married	HS	None	No	No	Oral
2	44	Married	HS	None	Yes	No	No
3	23	Married	HS	None	Yes	Yes	DMPA
4	42	Married	HS	HH	No	No	Oral
5	58	Married	Elementary	None	No	No	No

DMPA: Depot medroxyprogesterone acetate, HS: High school, HH: House helper

Table 2: Clinical and sexual history of patients diagnosed with vulvar intraepithelial neoplasia at a Tertiary Government Hospital from 2000 to 2012

Patient number	Presenting symptoms	Gravidity/parity	Age at 1st coitus	Number of sexual partners	Age at first delivery
1	Abnormal Pap	5/5	25	1	26
2	Vulvar pruritus	4/4	20	1	24
3	Vaginal discharge	2/2	20	1	20
4	Postcoital bleeding	4/4	20	1	21
5	Labial mass	5/5	25	1	26

Table 3: Physical examination findings and comorbid conditions in patients with vulvar intraepithelial neoplasia at a Tertiary Government Hospital from 2000 to 2012

Patient number	Location of the lesion	Gross findings	Comorbidity
1	Left labia majora, inferior aspect	Hyperpigmented	CIN III
2	Both labia majora, inferior aspect	Multiple hyperpigmented	Adenocarcinoma, cervix, Stage IB1
3	Labia majora, lateral margin	Solitary hyperpigmented nodule	CIN I
4	Both labia majora, superior aspect	Hyperpigmented nodules	None
5	Right labia majora from 6 to 8 O'clock position	Erythematous papule	None

CIN: Cervical intraepithelial neoplasia

Table 4: Pathologic findings and treatment in patients with vulvar intraepithelial neoplasia at a Tertiary Government Hospital from 2000 to 2012

Patient number	Pap smear	Histopathology	Colposcopy	Treatment received
1	CIN III	VIN II	HGL	Local excision
2	Normal	VIN I	N/A	Local excision
3	Normal	VIN I	LGL	Local excision
4	Normal	VIN I	LGL	Lost to follow-up
5	Normal	VIN III	Normal	Local excision

HGL: High-grade lesion, LGL: Low-grade lesion, VIN: Vulvar intraepithelial neoplasia, CIN: Cervical intraepithelial neoplasia, N/A: Not available

Pap smear was normal for all cases except for one who had a report of CIN III [Table 4]. Out of the four cases who underwent colposcopy, two cases had a low-grade lesion, one case had a high-grade lesion, and one case had a normal result. Histopathology of the lesions showed VIN 1 in three cases (60%), one case with VIN 2 (20%), and another case, VIN 3 (20%). All patients underwent local excision of the lesion while one case was lost to follow-up.

Discussion

Vulvar cancer is a rare malignancy representing approximately 4%–5% of all genital cancers in women. It occurs in about 2.5/100,000 women but is 2–3 times more frequent in developing countries. Currently, there are no screening tools for vulvar carcinoma.

This retrospective study aimed to determine the prevalence of VIN among outpatient gynecologic consults from the year 2000 to 2012 in a tertiary hospital setting. Five cases of VIN were confirmed by biopsy; hence, the prevalence of VIN for this study was 1.6/100,000 women per year over 12 years. This increase is most likely affected by the increasing prevalence of HPV infection in younger women which may induce multifocal precancerous epithelial lesions of the cervix, vagina, vulva, and anus.[13] However, it is important to note that not all intraepithelial neoplasia is associated with infection of HPV.

The small numbers in this study make subgroup analysis difficult; however, useful observations can be made from the data obtained.

The mean age of diagnosis is 42.2 years with a wide age range (median: 42 and age range: 23–58); most were in their fourth decade of life. This is consistent with previous studies that note peak incidence to be in women aged 45–49 years old.[8] Two out of the five cases consulted for vulvar complaints: One noted vulvar pruritus while another was able to palpate a vulvar lesion. The rest of the women were asymptomatic, which is typical of VIN. It was only during physical examination of the vulva that the disease was noted. The lesions were mostly described as hyperpigmented nodules on the posterior aspect of the labia majora. These disease characteristics are similar to those described in other studies: VIN was macroscopically visible and commonly seen on the posterior vulva and perineum which are common sites for vulvar carcinoma as well.[5] The disease was noted to be multifocal in three out of the five cases, two of which had concomitant CIN and one with cervical cancer. This is most likely associated with high-risk HPV infection; unfortunately, HPV DNA testing was not done due to financial constraints.

In addition to age, the low socioeconomic status appears to be associated with the disease. Socioeconomic status underlies three major determinants of health: health care, environmental exposure, and health behavior.[14,15] Patients with low socioeconomic status lack access to quality health care, especially in developing countries. Such patients are also more likely to reside and work in worse environments and experience greater residential crowding. As for health behavior, those with less education and less income are more likely to smoke, have sedentary lifestyles, and have poor nutrition.[14,15] These weaken the body's defenses and make one susceptible to infection. Less-educated women have poor health-seeking behavior since they are unaware when medical care is needed. All five patients were undergraduates, unemployed, and can be categorized as low socioeconomic status. Low socioeconomic status is associated with an increased risk for HPV infection and in turn, increases the risk for uVIN.

Smoking has been associated with VIN, whether it may be a history of current or former smoking.[16,17] Women who smoked were found to have, not only VIN but multicentric disease as well. The effects of smoking can be explained by the systemic effect of nicotine on the immune system, particularly, the Langerhans cells, affecting local immunity in the genital tract epithelium.[11,16] Women who continued to smoke after treatment were 30 times more likely to have persistent vulvar disease.[17] Only two out of the five cases were cigarette smokers, however, all five patients were exposed to secondhand smoke. Effects of secondhand smoke on VIN have yet to be investigated.

The currently accepted treatment for VIN is wide local excision,[10] although some authors also advocate laser therapy.[1,5] Our institution complies with this recommendation, having 80% of VIN cases undergo excision. An advantage of surgical excision is that a complete histologic assessment may be performed to exclude or define the diagnosis of occult invasive carcinoma.[9] Obtaining the specimen with a 0.5–1.0 cm disease-free margin is ideal to control symptoms and to avoid malignant transformation. Although the outcome is generally positive, the disease recurrence rate for this intervention is between 30% and 50%. Large excisions may lead to severe, deforming anatomic defects that particularly distress younger women with the disease. Hence, nonsurgical techniques, namely laser ablative therapy and imiquimod, are slowly gaining popularity especially since the prevalence of VIN has been increasing in younger women, particularly in developed countries.[9] However, these modalities are reserved for cases where the risk for progression is low and cancer is not suspected.

VIN is known to have high recurrence rates, exceeding 30%–50% with all treatment regimens.[4,10] The risk for recurrence is higher for those with positive excision margins. Since follow-up has been limited in most studies, ACOG stated that women with vulvar HSIL or uVIN should be considered to be at risk for recurrence and for vulvar cancer throughout their lifetime. Given the slow rate of progression, women are recommended to follow up 6–12 months after initial treatment, and then annually thereafter.[10] Although the efficacy of vulvar self-examination has not yet been proven prospectively, it appears prudent to advise patients to be vigilant for new lesions.

It is important to reiterate the value of primary prevention for VIN. Recent randomized control trials have demonstrated that sustained protection from VIN can be offered with a prophylactic HPV vaccine which is shown to prevent up to 70% of VIN. Immunization with the quadrivalent (HPV 6, 11, 16, 18) or 9-valent (HPV 6, 11, 16, 18, 31, 33, 45, 52, 58) HPV vaccine has been shown to decrease the risk of uVIN and should be recommended for girls aged 11–12 years with catchup through age 26 years if not vaccinated in the target age.[11]

Conclusion

Prompt diagnosis and appropriate treatment of VIN aim to prevent its progression to vulvar carcinoma. Although vulvar carcinoma is a rare condition, there has been a notable rise in the prevalence of VIN in recent years. Gynecologists should be vigilant and learn to identify premalignant lesions to prevent progression

to malignancy while also increasing awareness of the effect of socioeconomic and lifestyle factors on disease prevention.

Limitations

This study was limited by its retrospective design. The study yielded only a small population; therefore, only useful observations can be concluded to come up with a profile for our patients with VIN. Finally, the department of pathology has not yet adapted the new ISSVD nomenclature; hence, the use of terms VIN 1–3 in this study.

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Conflicts of interest

There are no conflicts of interest.

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