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Vulvar Intraepithelial Neoplasia: Our Experience on Diagnosis and Treatment

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ABSTRACT

Objective: The incidence of vulvar intraepithelial neoplasia (VIN) is increasing worldwide. The objective of this study was to describe our experience on the diagnosis and treatment of VIN in KK Women's and Children's Hospital (KKH), Singapore.

Methods: This retrospective study involved the review of clinical records of patients diagnosed with VIN in KKH over 5 years, from 1 January 2005 to 31 December 2009. The clinical records were reviewed until 31 March 2011.

Results: There were 21 cases of VIN. The mean follow-up duration was 25.7 months. VIN was classified as grade 1 in 5 patients (23.8%), grade 2 in 4 patients (19.0%) and grade 3 in 12 patients (57.1%.). The mean age of the affected patients was 50 years old. The majority were referred to our institution for vulvar lesion (9 cases, 42.9%) or vulvar condylomata (7 cases, 33.3%). The diagnosis of VIN involved careful visual assessment, colposcopy and colposcopic-directed biopsy. The therapeutic modalities were heterogeneous. Simple excision was used most frequently (6 cases, 28.6%), followed by laser vaporization and topical imiquimod 5% (Aldara, 3M Pharmaceuticals). During follow-up, the overall cure rate was 66.7%. Two out of the 3 cases that had failed treatment with persistent VIN were human immunodeficiency virus positive.

Conclusion: Early detection of VIN with visual assessment and biopsy is important to prevent vulvar cancer. Treatment is indicated for most cases of VIN. Patients with VIN should be considered at high risk of recurrent VIN and vulvar cancer. Therefore, long-term follow up is essential, ideally in a specialized gynaeoncological centre.

Keywords : Vulvar intraepithelial neoplasia, diagnosis, treatment

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INTRODUCTION

The incidence of VIN is increasing worldwide, especially among women in their 40s. The VIN incidence multiplied more than four-fold between 1973 and 2000 in the United States [1]. In 2004, the International Society for the Study of Vulva Disease (ISSVD) subcommittee on

oncology dropped the term VIN 1, as the cytopathic changes diagnosed in VIN 1 were non-specific, often representing normal skin, superficial trauma, or self-limiting infection caused by human papillomavirus (HPV) [2]. Therefore, it is widely accepted that VIN 1 should be managed conservatively. In contrast, VIN 2 and VIN 3 lesions express the p16 (INK4a) protein and should be treated as these lesions have potential for malignant transformation [3]. In the current system [2], VIN is subdivided into usual-type VIN (including warty, basaloid and mixed VIN) and differentiated VIN. However, for the purpose of this study, the old grading classification recommended by the ISSVD in 1986 [4], dividing the squamous intraepithelial lesions of the vulva into VIN 1, VIN 2 and VIN 3, will be used, as this three-grade classification is still being practiced in our institution.

The aim of this retrospective study was to describe our experience on the diagnosis and treatment of VIN in our institution.

METHODS

This retrospective study entailed a review of the clinical records of all patients diagnosed as having VIN at KKH over 5 years from 1 January 2005 to 31 December 2009. The records were periodically reviewed through to March 31, 2011.

The diagnosis of VIN involved direct visualization of the lesion via colposcopic examination, along with the application of 5% acetic acid solution for the acetowhite test to define the site of lesion; and when indicated, a biopsy of the lesion followed by a histologic evaluation. The biopsies were taken with a Keyes biopsy instrument. The biopsy slides were reviewed by the pathologists in our institution and the positive results were graded as VIN 1, VIN 2 or VIN 3.

The follow-up evaluations consisted of a colposcopic examination and a biopsy, if indicated. Following treatment, the lesions were considered cured if the findings of the colposcopic examination were normal at the 6-month evaluation, and they were considered persistent (meaning that the treatment had failed) if they were still present at that time. They were considered recurrent if they appeared to be cured at 6 months but reappeared later.

There was no ethics review or informed consent required in this study as this was a retrospective audit within the institution.

RESULTS

There were 21 cases of VIN diagnosed over the 5 years; 4 cases were diagnosed in 2005, 4 in 2006, 3 in 2007, 6 in 2008 and 4 in 2009. Table 1 shows the principal characteristics of these patients. The mean age of the affected patients was 50 years old. The mean follow-up duration was 25.7 months. All 21 patients were non-smokers. According to the traditional ISSVD three-grade classification [4] (still practiced in our institution), VIN was classified as grade 1 in 5 patients (23.8%), grade 2 in 4 (19.0%) and grade 3 in 12 (57.1%.). There were 4 VIN patients diagnosed with concurrent CIN, 1 VIN patient with concurrent vulvar cancer, 1 VIN patient with concurrent vaginal intraepithelial neoplasia (VaIN) and 1 VIN patient with concurrent cervical cancer. Out of the 21 patients, only 13 cases had the HPV Digene test performed; 7 cases had positive results, while the remaining 6 cases had negative results.

The majority was referred to our institution because of vulvar lesions (9 cases, 42.9%) or vulvar condylomata (7 cases, 33.3%). The remaining patients were referred to us for vulvar itching/ irritation (1 case, 4.8%), vulvar ulceration (1 case, 4.8%) and abnormal Pap smears (3 cases, 14.3%).

The diagnosis of VIN involved careful visual assessment, colposcopy and colposcopic-directed biopsy. During colposcopy, 10 cases (47.6%) were found to have unifocal pathology, while 11 cases (52.4%) had multifocal pathologies. The majority of the VIN lesions were found on the labia (19 cases, 90.5%), while the remaining 2 cases were on the fourchette. Six out of the 9 cases of vulvar lesions were pigmented.

The therapeutic modalities were heterogeneous. For lesions ranging from VIN 1 to 3, simple excision was used most frequently (6 cases, 28.6%), followed by laser vaporization (5 case, 23.8%) and topical imiquimod 5% (Aldara, 3M Pharmaceuticals), (5 cases, 23.8%). Two cases (9.5%) underwent superficial vulvectomy and another 2 (9.5%) underwent wide local excision for treatment; all these 4 cases had VIN 3. Another 3 cases had conservative treatment with close follow-up colposcopy. Interestingly though, all these 3 cases which were managed expectantly were not VIN 1, but at least VIN 2 lesions. One case defaulted treatment.

During follow-up, the overall cure rate in this audit was 66.7%. Eleven cases were cured after treatment (52.4%) and the 3 cases that opted for conservative management spontaneously regressed (14.3%). All the VIN cases with failed treatment or recurrent disease had multifocal disease.

Two out of the 3 cases that had failed treatment with persistent VIN were human immunodeficiency virus (HIV) positive on anti-retroviral therapy. The first HIV patient had persistent VIN 3 despite laser vaporization. She was then offered skinning vulvectomy, but declined

this treatment and opted for topical imiquimod 5% application 3 times a week. During her latest colposcopy follow-up (after being on 8 months of topical imiquimod 5%), there were still dense acetowhite changes on the vulva and histological re-biopsy revealed VIN 3. She was then advised to continue the topical imiquimod 5% application till the next follow-up appointment. The other HIV patient had multifocal labial lesions with a histological biopsy of VIN 3. She declined surgical treatment and had been on topical imiquimod 5% application 3 times a week. Despite being on this treatment for a total of 3 years, colposcopy and re-biopsy still showed persistent VIN 3.

The remaining case which had failed treatment had multifocal vulvar condylomata with a histological biopsy of VIN 3. She had persistent disease despite laser vaporization, and hence underwent simple excision of the VIN. However, the margins of the excision tissue sample was involved and as expected, the VIN disease persisted. She was finally cured after undergoing wide local excision of the lesion.

Two patients (9.5%) had recurrent disease. The first patient had 3 labial condylomata with VIN 1 on histology. She underwent simple excision of the condylomata. Unfortunately, there were condylomata seen on colposcopy about a year later and re-biopsy showed VIN 1. This particular patient subsequently defaulted follow-up. The other patient with recurrent disease was initially diagnosed with extensive multifocal labial condylomata with a histological biopsy of VIN 1. She underwent laser vaporization. At 8 months post - treatment, she developed recurrent disease and was cured after liquid nitrogen spray. There were 2 cases which defaulted follow-up after treatment.

DISCUSSION

The patients diagnosed with VIN in this study were on average older than those diagnosed with cervical dysplasia, in agreement with the literature [5, 6]. VIN affected women over a wide age range in this study: from 23 to 86 years old. As reported by Hillemanns P et al [6] and Reich O et al [7], our study confirmed that a large number of these patients had a history of CIN, ValN, vulvar or cervical cancer. Since VIN may coexist with CIN, every woman who had an abnormal Pap smear should have an examination of the vulva. All the cases with failed treatment or recurrent disease had multifocal disease, suggesting that multifocality was a risk factor for persistent or recurrent disease, as supported by others in the literature [6]. The other risk factor for recurrence of VIN was the prevalence of high risk HPV DNA status [6]. However, this was not portrayed in this current study due to its small sample size.

The distribution of grades of VIN in our study was in congruent with that reported by the Italian Study Group on Vulvar Disease [8], who stated that there were most cases of VIN 3, followed by VIN 1 and then VIN 2.

Munoz and colleagues [9] have proven that immunization with the quadrivalent HPV vaccine, which is effective against HPV genotypes 6, 11, 16 and 18, decreases the risk of VIN and should be recommended to women in the target populations. Cessation of smoking should be encouraged as it is associated with VIN. Surprisingly, none of the patients in this study were smokers.

Currently, there are no screening strategies for the prevention of vulvar cancer through early detection of VIN. Diagnosis of VIN is performed via meticulous visual assessment during colposcopy and biopsy of the vulvar lesions.

In our institution, the majority of these women were referred to us for vulvar condylomata or other vulvar lesions. Direct visualization via colposcopic examination should be performed thoroughly to identify the location, number and size of lesions with the aid of 5% acetic acid. The Schiller's test should be routinely performed to increase the yield of the procedure. The diagnosis of VIN would be confirmed by the histology of colposcopic-directed biopsy. Pigmented vulvar lesions should always be biopsied.

Treatment is indicated for most cases of VIN. The overall cure rate in this audit was 66.7%. The overall recurrence rate after treatment was 9.5% for a mean follow-up duration of 25.7 months. This figure was lower than that reported by others [6], but this discrepancy may again be due to the small sample size in this study.

VIN 1 usually reflects a self-limiting infection caused by HPV and hence, conservative management with follow-up colposcopy and biopsy is acceptable. Interestingly though, all the 3 cases managed conservatively in this study were not VIN 1, but at least VIN 2 lesions, which spontaneously regressed. However, this does not imply that conservative management should be routinely offered to patients with VIN 2 and 3 lesions, as this may just be a coincidental spurious result due to small sample size.

In this study, simple excision was the most frequently used therapeutic modality, followed by laser vaporization and topical imiquimod 5% application. Wide local excision is recommended when cancer is suspected. When occult invasion is not a concern, VIN can be treated with simple excision, laser vaporization or application of imiquimod 5%. Excision has been considered the treatment of choice, mainly because it provides a specimen for histologic review and the risk of recurrence may be lower as compared with that of laser

vaporization [10]. Topical imiquimod 5% application 3 times a week until the lesions are cleared is effective for the treatment of VIN [11]. However, this has associated adverse effects of erythema and vulvar pain. Post-treatment, residual lesions will require surgical treatment. Skinning vulvectomy involves removing all vulvar skin is rarely required. It is useful in cases of extensive, multifocal lesions especially in immunocompromised patients and recurrent disease.

Patients with VIN should be considered at high risk of recurrent VIN and vulvar cancer throughout their lifetimes [5, 6]. Therefore, long-term follow up is essential, ideally in a specialized gynaeoncological centre.

In view of the small sample size, a follow-up 10-year case series with a larger sample size will add value to the results presented in this study. Other drawbacks in this retrospective audit included the difficulty in defining treatment failure in VIN treatment. This was because the difference between local persistence/relapse versus the development of new lesions on the vulva could not always be ascertained retrospectively. Another weakness of this study was selection bias. The treatment modalities chosen were at the decision of the surgeon.

CONFLICT OF INTEREST

No known conflict of interest.

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Table 1. Principal characteristics of patients

No.	Age at Dx	Parity	Smoking	HPV Dig	CIN/VaIN/Ca	Symptoms	Histo	Stage Date	Treatment (Rx)	F/U	F/U in Mths
1	25	1	No	Pos	Nil	Vulvar condylomata	VIN I	2005	Laser vap + simple excision	Cured	12
2	68	0	No	Neg	CIN, VaIN, Ca Cx	Abnormal pap	VIN III	2008	Simple excision	Cured	36
3	51	2	No	Pos	Nil	Vulvar condylomata	VIN III	2005	Laser vap + simple excision	Failed Rx-persistent	35
4	65	6	No	Neg	Nil	Vulvar itching, irritation	VIN III	2008	Aldara cream x 6 wks + sup vulvectomy	Cured	30
5	82	8	No	Neg	Nil	Vulvar lesion	VIN III	2005	Simple excision	Cured	23
6	23	0	No	Nil	Nil	Vulvar condylomata	VIN I	2006	Laser vap	Recurrence < 1yr	13
7	29	0	No	Pos	CIN 2	Vulvar condyloma	VIN II	2006	No rx	Spontaneous regression	26
8	35	0	No	Neg	Nil	Abnormal pap	VIN III	2008	Aldara cream	Cured	35
9	32	0	No	Pos	Nil	Vulvar condylomata	VIN I	2009	Simple excision	Recurrence <1yr	4
10	86	0	No	Neg	Nil	Vulvar lesion	VIN III	2006	Wide local excision	Cured	12
11	56	4	No	Neg	Nil	Vulvar lesion	VIN III	2005	Wide local excision	Cured	68
12	50	1	No	Nil	CIN 2	Abnormal pap	VIN III	2007	Laser vap	Failed Rx-persistent	45
13	59	3	No	Nil	Nil	Vulvar lesion	VIN III	2007	No rx	Spontaneous regression	10
14	24	1	No	Nil	Nil	Vulvar lesion	VIN II	2006	No rx	Spontaneous regression	28
15	37	0	No	Nil	Nil	Vulvar lesion	VIN III	2008	Aldara cream	Failed Rx-persistent	23
16	37	0	No	Nil	Nil	Vulvar condylomata	VIN II	2008	Aldara cream	Defaulted	2
17	76	7	No	Pos	Nil	Vulvar lesion	VIN III	2009	Planned for wide local excision	Defaulted rx	<1
18	52	3	No	Pos	CIN 3	Vulvar lesion	VIN I	2009	Simple excision	Cured	19
19	52	2	No	Nil	Nil	Vulvar lesion	VIN III	2007	Sup vulvectomy	Cured	44
20	57	3	No	Nil	Ca vulva	Vulvar ulceration	VIN II	2008	Aldara cream	Cured	29
21	53	0	No	Pos	Nil	Vulvar condylomata	VIN I	2009	Laser vap	Cured	19

Dx =Diagnosis
HPV Dig = HPV Digene Test
CIN = Cervical intraepithelial neoplasia
VaIN = Vaginal intraepithelial neoplasia
Ca Cx = Cancer of cervix
Ca Vulva = Cancer of vulva
Histo =Histology
Vap = Vaporization
Sup = Superficial
F/U = Follow-up
Mths = Months