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CLINICAL ARTICLE

HPV-related vulvar intraepithelial neoplasia: Outcome of different management modalities

I. Bruchim [a,b], W.H. Gotlieb [a,b], S. Mahmud [c], E. Tunitsky [a,b], K. Grzywacz [a,b], A. Ferenczy [d,b,*]

[a] *Division of Gynecologic Oncology, Sir Mortimer B. Davis-Jewish General Hospital, Montreal, Quebec, Canada*
[b] *McGill University, Montreal, Quebec, Canada*
[c] *Department of Community Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada*
[d] *Department of Pathology, Sir Mortimer B. Davis-Jewish General Hospital, Montreal, Quebec, Canada*

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Abstract

Objective: To evaluate the outcome of various management schemes for HPV-related vulvar intraepithelial neoplasia (VIN, usual type). *Methods:* Retrospective chart review of patients with histologically diagnosed grade 2/3-VIN who had at least one year of follow-up. The variables that were collected included patient characteristics, management modalities, and clinical outcome. *Results:* Fifty patients with a median age of 45 years old were evaluated. The median duration of follow-up was 43.5 months (12–186). Complete response (CR) and partial response occurred in 28 (56%) and 4 (8%), respectively. Nineteen of 28 patients with CR recurred with VIN. Surgical excision yielded higher CR (77%) than did either ablational techniques (21–33%) or topical immunotherapy (33%). *Conclusion:* In this experience, surgical excision for VIN, usual type, resulted in better therapeutic success rates than other treatment modalities. Management schemes should be individualized based on extent of disease and patient compliance.

1. Introduction

Vulvar intraepithelial neoplasia (VIN) is a premalignant lesion involving mostly the non-hairy skin of the vulva. There are two distinct types, namely HPV-related (HPV/VIN) and HPV-unrelated VIN. The former is by far the most frequent variant of vulvar cancer precursors and is caused by high-risk HPV (HR-HPV) types, primarily 16, 18, and 31. Histologically, it is made of poorly to undifferentiated basal cells and/or highly atypical squamous epithelial cells involving the entire

* Corresponding author. Department of Pathology, SMBD-Jewish General Hospital, 3755 Cote Sainte-Catherine Road, Montreal, Quebec, Canada, H3T 1E2. Tel.: +1 514 340 7526; fax: +1 514 340 7542.
E-mail address: alex.ferenczy@mcgill.ca (A. Ferenczy).

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thickness of the epithelium with or without a warty, hyperkeratotic surface. Current terminology refers to this type of cancer precursor as VIN, usual type. It occurs in young and mid-adult women, tends to be multifocal, appears pigmented, whitish/reddish or a combination of all these three color tones, and carries the same demographic risk factors as those observed in women with cervical intraepithelial neoplasia (CIN) [1]. In fact, about 50% of such lesions are associated with high-grade lesions of the cervix and less often, of the vagina. The progression to invasion potential in treated patients is on the order of 3% and 9% in their untreated counterparts according to a review of over 3000 cases published in the literature [2]. However, progression to invasion has been reported by some at a much higher rate in untreated cases and most investigators feel that treatment is indicated, particularly in symptomatic patients [3]. The management options are multiple, testifying to the fact that none of them is truly satisfactory as the various treatments are notorious for high failure and recurrence rates. Treatment protocols use either surgical excisional procedures including partial superficial (skinning) vulvectomy, loop electrosurgical excision procedure (LEEP), or ablations using CO_2 laser vaporization, electrofulguration or still, a variety of off-label medical therapies including topical 5% 5-fluorouracil (Efudex™, Valeant Pharmaceuticals, Costa Mesa, CA) and most recently, self-applied, home immunotherapy with 5% imiquimod cream (Aldara™, 3M Pharmaceuticals, St-Paul, MN). The latter seems to be particularly attractive for the majority of HPV/VIN occurs in younger women in whom preservation of lower genital anatomy is crucial [4]. The other form of VIN is seldom associated with HR-HPV types. Histologically it is well-differentiated, hence the name "VIN, well-differentiated type". It occurs in the elderly within areas of auto-immune vulvar dermatoses such as squamous cell hyperplasia (lichen simplex chronicus) or lichen sclerosus. The lesion tends to be unifocal and is most often located adjacent to well-differentiated, keratinizing squamous cell carcinoma. Many patients suffer from chronic, longstanding itch–scratch–itch cycles as a result of subepithelial dermal inflammation. The aim of this retrospective study was to evaluate the clinical outcome of patients with HPV-related VIN managed and followed at the colposcopy clinic in our institution.

2. Patients and methods

The histological reports of all the women diagnosed and treated for VIN at the colposcopy clinic at the SMBD-Jewish General Hospital, Montreal, Canada from 1985 to 2004 were retrieved. Only patients who were either treated for the first time with only one single therapeutic modality or simply followed without treatment in our colposcopy clinic, and had at least one-year duration of follow-up were included in the evaluation. Patients treated elsewhere and consulted for recurrent VIN as well as those with VIN, well-differentiated type, were excluded from the study. Post-treatment follow-up protocol included colposcopic assessment every 4–6 months in the first 2 years. Therefore, all patients included in the study had at least 1 documented follow-up during the first year after therapeutic intervention. Those who were simply followed after histological ascertainment were seen at 6-month intervals and biopsy was repeated in these patients only if any lesional area was suspicious for incipient invasive disease. In all patients who were treated, punch biopsies were performed prior to therapy. The histological diagnosis of basalo-warty VIN was made according to the recently revised VIN terminology proposed by the International Society for the Study of Vulvovaginal Disease (ISSVD) [5]. Therefore, lesions referred to as VIN 1 were excluded and VIN 2 and 3 were combined into a single category, VIN, usual type.

Patient characteristics were retrieved from the charts including age, number of sex partners, smoking and history of CIN or vaginal intraepithelial neoplasia (VAIN). Data relating to symptoms versus no symptoms as well as anatomical location, i.e. hairy versus non-hairy skin of the vulva, disease extent (total lesional area measured in centimeters), type (multifocal versus single or confluent), and response to management schemes (treatment or follow-up without treatment), were abstracted from the medical records. Complete response (CR) was considered as no clinical and colposcopic evidence of any vulvar lesion, partial response (PR) was considered as reduction of total VIN area by more than 50%, and no response (NR) was defined as persistent disease (>50%) including increase in overall vulvar skin involved with pre-existent and/or new lesions after one year of follow-up. Recurrence (R) was defined as development of new lesional epithelium in complete responders.

3. Statistical analysis

Differences in response rates between the different groups were tested using Chi-squared test or Fisher exact test if table included small (<5) numbers.

4. Results

The study included 50 patients. Twenty-five women (50%) complained of intermittent pruritus and/or burning discomfort of 6 months or longer duration; the remaining patients were asymptomatic. By histology, 10 patients had pure basaloid lesions, whereas 40 had basalo-warty VIN. The mean age of the patients was 44.7±10.8 years, and median age was 45 years. There were 9 (18%) patients younger than 35 years and 10 (20%) older than 55 years. Thirty patients (60%) were past or current smokers, and 23 (46%) of the patients had more than two lifetime sex partners prior to their first visit at our colposcopy clinic. Of the 50 patients, 17 (34%) and 7 (14%) patients had a history of CIN 1 to 3, and high-grade VAIN 2/3, respectively. In 22 (44%) patients, the lesions were multifocal and the most common affected sites were the non-hairy skin of the vulva (68%), followed by the hairy skin of the labia majora and perineal and peri-anal skin. Intra-anal involvement was not encountered. The patients'

Table 1 Patients characteristics, $N=50$

Median age at diagnosis (years)	45 (25–72)
Age<35 years old	9 (18%)
Age>56 years old	10 (20%)
Sex partners>2 [a]	23 (66%)
Smoker	30 (60%)
Previous CIN	17 (34%)
Previous VAIN	7 (14%)
Multifocal VIN	22 (44%)

[a] Missing info—15 pts.

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Table 2 Response to the different treatment modalities, at 1 year of follow-up

Treatment	Complete response, *n* (%)	Partial response, *n* (%)	No response, *n* (%)	Recurrence, [a] *n* (%)	Overall complete response, [b] *n* (%)
Surgical, *n*=13	11 (84.6)	1 (7.7)	1 (7.7)	1 (9.1)	10 (77) [c]
LEEP, *n*=14	10 (71.4)	0	4 (28.6)	7 (70)	3 (21)
Laser, *n*=9	4 (44.5)	1 (11.1)	4 (44.4)	1 (25)	3 (33)
Imiquimod cream, *n*=9	3 (33.3)	2 (22.2)	4 (44.4)	0	3 (33)
No treatment, *n*=5	0	0	5 (100)	N/A	0
Total, *n*=50	28 (56)	4 (8)	18 (36)	9 (32.1)	19 (38)

N/A = not applicable.
[a] In the 28 patients with complete response.
[b] Includes recurrences in complete responders.
[c] *P*=0.010.

characteristics are featured in Table 1. There was no correlation between patients' characteristics including age, smoking status, number of sex partners and previous CIN or VAIN and failure and/or recurrence rates in the different treatment groups.

Treatment modalities included local surgical excision in 8 patients, superficial skinning vulvectomy in 5, LEEP (both excision and fulguration) in 14, CO_2 laser vaporization in 9, self-applied topical home therapy with 5% imiquimod cream (Aldara™) in 9, and 5 patients were followed without treatment. Both LEEP and CO_2 laser vaporization were performed under colposcopic guidance, whereas surgical excisions were carried out under general anesthesia. Electroexcision was performed for the purpose of "mini-debulking" in cases of extensive, raised disease. Electrofulguration and CO_2 laser vaporization were applied to both hairy and non-hairy skin lesions for flat lesions, including those which were adjacent to previously electroexcised raised lesions. Depth of denudation did not exceed 1 mm (first surgical plane or papillary dermis with a chamois appearance) including hairy skin disease. Depth was controlled by performing procedures at high magnification. In our experience, depth involvement of the pilosebaceous system by VIN is less than 1 mm in 97.7% of cases [6]. Indication for surgical excision was extensive, confluent disease exceeding 20 cm^2 total skin area, whereas ablational therapy with electrosurgery and CO_2 laser was carried out in patients with multifocal disease not exceeding 20 cm^2 total skin area of the vulva/perineum and peri-anal skin. Home immunotherapy with 5% imiquimod cream (Aldara™) was offered to patients with multifocal lesions limited to 10 cm^2 or less of total hairy and non-hairy skin area involved. Patients who were not treated preferred to be followed at regular intervals on a long term basis. None of the surgically excised specimens contained invasion of the stroma/papillary dermis. Eighteen of 50 (36%) patients were subjected to therapy combining at the same treatment session, excision and ablation. In all patients treated with imiquimod (Aldara™) immunotherapy was used as a first-line treatment approach for the purpose of either decreasing total disease volume or achieving complete response.

The average duration of follow-up was 54.5±40.1 months (12–186) with a median of 43.5 months. The median follow-up of patients treated by surgical excision was 37 months (12–108), of those treated by LEEP—76.5 months (12–116), laser—36 months (12–186), 5% imiquimod cream (Aldara™)—29 months (12–55) and the untreated group—39 months (12–81). The mean frequency of 5% imiquimod cream (Aldara™) application per week was 1.53±0.77 (1–3) and the mean duration of application was 10.6±6.99 weeks (4–28). Treatment with 5% imiquimod cream (Aldara™) was well tolerated in 7 of 9 patients on a regimen of once-a-week application for 8 weeks, while two patients complained of severe burning at application sites. Both of these patients failed to respond to topical immunotherapy with one of the two women experiencing expanding disease.

The response rates are summarized in Table 2. Total response rates (complete and partial) assessed at one year of follow-up for all patients in the different groups, including those who received no treatment, were 64%. Overall response rates were 92.3% in the surgical treatment group, 71.4%, 55.6%, and 55.5% in those treated with LEEP, laser and 5% imiquimod cream (Aldara™), respectively (*P*=0.174). All patients without treatment had persistent or expanding VIN at one-year follow-up. None of the post-treatment, persistent VIN increased in size during follow-up in the surgical treatment group, while 20% in both the 5% imiquimod cream (Aldara™) and no treatment groups had either expanding (15%) or additional or new area (5%) VIN at one year. Among complete responders, a total of 9 patients experienced recurrence with average time to recurrence of 29±26.7 months and a median of 16 months. Recurrences occurred with equal frequency in the hairy and non-hairy skin and rates were lowest in surgically treated patients—1 of 11 (9.1%), and the highest in those treated with LEEP—7 of 10 (70%) (*P*=0.008). One patient in the laser-treated group experienced recurrence while none recurred in the 5% imiquimod cream (Aldara™)-treated group. Treatment failure and recurrent disease, combined, were observed in 27 patients, namely 2 of 13 (15.3%) in the surgically treated group, 11 of 14 (78.6%) in the LEEP-treated group, 5 of 9 (44.4%) in the CO_2 laser-treated group, 4 of 9 (44.5%) in the 5% imiquimod cream (Aldara™)-treated group (*P*=0.004). Conversely, the overall CR (including recurrences) was significantly better in the surgically treated group (77%) compared to all other treatment modalities (*P*=0.010) or the follow-up only group.

5. Discussion

The current experience includes 50 patients with histologically verified VIN, usual type, managed either with a variety

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of single treatment modalities or only colposcopic follow-up at 6-month intervals. At one-year follow-up, the total response rate (complete and partial) for all management modalities including follow-up without treatment was 64%. The complete response rate was highest in the surgically treated group and also had the lowest recurrence rate, 84.6% and 9.1%, respectively. LEEP resulted in a high complete response rate in the order of 71.4%, however, it was associated with the highest recurrence rate of 70% ($P=0.008$). The mean follow-up of the LEEP group was significantly longer compared to the other groups which can, at least, partially explain the significantly high recurrence rate in this group. Treatment with CO_2 laser vaporization or topical 5% imiquimod cream (Aldara™) was associated with relatively low complete response rates. However, only one of nine patients recurred in the CO_2 laser and none recurred in the imiquimod cream (Aldara™) group. Although the most favorable response was observed in patients treated with surgical excision, the overall response rates between treatment groups failed to reach statistical differences due to the small number of patients in each group. When the recurrence rates are included in the overall cure rates (CR), the CR for the entire group of 50 women was 38%. Surgical excision still performed better (77% CR) than any other treatment modality used (22% to 35%). The mean time to recurrence in this experience was 29 months, with the shortest time interval post-therapy occurring at 3 months and the longest about 5 years. The follow-up only arm has not been proven to be a useful management option in this study, as none of the patients had spontaneous regression.

Complications related to the different treatments delivered were low on the order of 5% and included post-operative healing-related pain being the greatest in the LEEP/laser-treated groups and the lowest in the excisional group. Application-site severe burning pain prevented the continued use (over 4 weeks) of imiquimod 5% cream (Aldara™) in 2 of 9 patients. One patient developed scarring with hypo- and hyperpigmentation of the CO_2 laser-treated skin. None of the patients complained of post-treatment sexual dysfunction. Patients who failed and/or recurred after therapy tended to have multifocal lesions and one patient was immunosuppressed. Co-existent CIN/VAIN or peri-anal intraepithelial neoplasia (PAIN) did not seem to influence treatment results of vulvar lesions.

Our results corroborate previous studies which also found relatively high failure and recurrence rates in patients treated with ablation or topical immunotherapy compared to primary, either local excision or for extensive VIN, skinning vulvectomy [7]. Hillemanns et al. reported recurrence rate of 39.8% in a review of 93 patients with VIN [8]. The recurrences rate was highest after laser therapy (48.1%), while none of the 7 patients treated by vulvectomy experienced a relapse. There was one progression to vulvar cancer. The therapeutic effectiveness of LEEP compared to CO_2 laser was studied by Ferenczy et al. in 28 patients with VIN and they reported overall complete response of 48% with recurrence rate of 52% after either a single LEEP or laser treatment [1]. In contrast, van Seters et al., in a systemic review of the literature encompassing 3322 cases of VIN, found recurrence rates of 18%–23% with no statistical difference between vulvectomy, partial vulvectomy, local excision and laser vaporization, however, the recurrence rate was highest after cryotherapy (56%) [7]. Recurrence rates of VIN treated with CO_2 laser vaporization versus surgical excision were also found to be the same in the experience of Jones et al. [3]. Mcnally et al. reported a retrospective review of the management of VIN III in 101 patients [9]. The mean duration of follow-up in their study was 36 months. Wide local excision was the most frequent used treatment modality (78%). Thirty eight percent of their patients required at least one further treatment for recurrent disease.

Imiquimod 5% cream (Aldara™), an immune response modifier, has been used successfully to treat anogenital warts [4]. Imiquimod (Aldara™) induces cell-mediated Th-1 response against low oncogenic risk HPV 6/11-associated disease. Recently, a series of small, uncontrolled pilot studies reported the off-label use of imiquimod (Aldara™) in the treatment of VIN 1 to 3 [7,10–15]. A total of 83 patients mainly with localized, "limited" size disease were treated with imiquimod cream (Aldara™), with an overall complete response rate of 43% and total complete/partial response rates of 72% [10]. In this study, self-applied imiquimod (Aldara™) immunotherapy applied 3 times per week for up to 3 months was well tolerated. In our experience, however, immunotherapy was associated with acceptable adverse events such as burning pain when applied once, maximum twice a week and no patient tolerated therapy longer than 8 weeks.

The progression potential of HPV-related VIN is controversial ranging from less than 3% to 80%. Zawislak et al., in a recent study documented a 20% progression rate to invasive vulvar squamous cell cancer in 90 patients treated for VIN [16]. The mean time to progression to invasive cancer was 35 months, while 39% (7/18) of these patients were diagnosed with invasive disease within 12 months of initial diagnosis. The authors suggested that inadequate diagnosis and/or treatment of pre-existent invasive disease may explain their own and other authors' high "progression" to invasive cancer rates. In the experience of Jayne and Kaufman, two patients treated for VIN with topical imiquimod (Aldara™) were found, respectively, with pre-existent and probably invasive squamous cell carcinoma of vulva [15]. Similarly, a patient was recently sent to our colposcopy clinic with a FIGO Stage II vulvar cancer who was treated by a dermatologist with imiquimod (Aldara™) for "clinically classic Bowen's disease". Because of no response to treatment, a biopsy was eventually performed and a definite diagnosis of invasive cancer was made. The case emphasizes the importance of securing histological confirmation to rule out pre-existent invasion prior to embarking on conservative therapy.

In the van Seters et al. meta-analysis, only 9% of untreated patients progressed to invasive carcinoma, while the rate of progression in treated patients was 3% [2].

None of our patients with partial or no response to therapy as well as those who were untreated progressed to invasive cancer during a mean follow-up of 44 months. This might be related to the small number of patients in this study and also to selection bias since all patients had close surveillance at the colposcopy clinic and those who failed initial treatment or had recurrence, were treated with a different treatment modality with no significant delay. Also, those patients who wished to be followed rather than treated at the time of initial diagnosis were subjected eventually to some form of disease removal. The reason for the latter was to relieve symptoms (pruritus, burning) and/or fear of eventually progressing to cancer.

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This study has several limitations as it has the inherent weaknesses of a retrospective, non-randomized, non-controlled, case-series evaluation. Although all patients had at least one-year follow-up, the length of total follow-up periods varied greatly from one treatment group to another. The longest follow-up was for the LEEP group whereas the shortest was for those treated with 5% imiquimod cream (Aldara™). This could have biased the follow-up data results with respect to recurrence rates. Higher recurrences are naturally expected with longer follow-up duration. Recurrence rates were only assessed statistically in CR patients, while those occurring in PR's were considered "expanding" lesions. This resulted in lower than the true rates of total recurrences. However, from a clinical point of view, treatment of patients with PR has to be carried out whether or not persistent lesion is associated with recurrences. Only the size of treatment field may vary. In contrast, in CR's, only the recurrent lesions are treated. Moreover, the number of patients in each group was relatively small and the statistical difference in response rates could only be made between the surgical group and all the other management modalities, although there was a trend for improved outcome after surgical treatment. In patients with multifocal, small-sized lesions, it seems that either laser vaporization or electrofulguration may be the treatment of choice to avoid excessive tissue removal associated with excisional techniques. Self-applied home immunotherapy with 5% imiquimod cream (Aldara™) may also be offered as either a first or second line treatment for localized VIN. However, for extensive disease and those who failed conservative ablational or topical immunotherapy, surgical excision is the most appropriate therapeutic approach.

It is clear that current treatments for VIN are suboptimal and continue to represent a clinical challenge. This is particularly true for a substantial proportion of VIN occurs in young and mid-adult women who wish to preserve intact anogenital anatomy. The best approach is toward individualized management schemes based on clinical presentation (symptomatic versus asymptomatic), extent of disease involvement and patient preference.

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