High-grade vaginal intraepithelial neoplasia – review of 23 cases
Neoplasia intraepitelial vaginal de alto grau – revisão de 23 casos

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Abstract

Overview and aims: Vaginal intraepithelial neoplasia (VaIN) is a rare disease, not yet completely characterized. The aim of this study is to determine possible risk factors for development and progression of VaIN and to assess the most effective management procedure.
Study Design: Retrospective study.
Population: All patients with high-grade VaIN managed at our department between 1994 and 2012.
Methods: Individual case files were reviewed. Demographic characteristics, general and gynecologic medical history, methods of diagnosis, lesion characteristics, treatment procedures and outcome were statistically analysed.
Results: Twenty-three high-grade VaIN (65% VaIN 3 and 35% VaIN 2); mean age at diagnosis of 57 years; 17% potentially immunossupressed; 74% with previous hysterectomy, 76.5% due to malignancy and 23.5% due to benign disease, with longer delay between such procedure and the VaIN diagnosis in the last group (average: 7.5 *versus* 19.7 years); 83% with associated cervical neoplasia; four with high-risk human papillomavirus (HR-HPV) infection among 5 tested.

Six patients were treated by laser ablation, with 3 (50%) remissions, 1 (17%) persistence and 2 (33%) relapses. Ten patients were treated by excision, with 7 (70%) remissions, 1 (10%) persistence and 2 (20%) progressions to squamous cell carcinoma (SCC). Five patients were treated by colpectomy, with 3 (60%) remissions and 2 (40%) persistences. Two remaining patients missed treatment and appointments: one had remission and the other progressed to SCC. Patients with lesion persistence, relapse or progression after treatment had some possible risk factors such as immunossupression, HR-HPV infection or associated cervical neoplasia.
Conclusions: Despite the reduced sample size, the present study suggests some possible risk factors for the development of high-grade VaIN and poor outcomes after treatment. Furthermore, it supports the maintenance of a long term cytologic screening after hysterectomy and the treatment of high-grade VaIN over expectant approach.

Keywords: VaIN; Risk factors; Treatment; Outcome.

OVERVIEW AND AIMS

Vaginal intraepithelial neoplasia (VaIN) accounts for only 0.4% of lower genital tract intraepithelial disease[1,2], annually affecting from 0.2 to 2 per 100.000 women[3], and it is generally asymptomatic[4,5].

Therefore, this disease is not well characterized, its natural history is poorly understood, as well as the potential of progression to invasive squamous carcinoma[4], and there is scarce information about the effectiveness of each treatment modality[5].

Evidence supports, however, that risk factors for the development of VaIN are similar to those found in cervical intraepithelial neoplasia (CIN): High-risk strains of human papillomavirus (HR-HPV) infection[2,6], with HPV 16 being the most frequent subtype[7,8]; synchronous or previous lower genital tract neoplasia[3]; previous hysterectomy, mainly when performed for treatment of malign disease[2]; history of pelvic irradiation[2]; immunosuppression, mainly HIV infection[3,6]; *in uterus* diethylstilbestrol exposition[3]; and cigarette smoking[9].

VaIN is thought to be a precursor to malignant di-

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sease[2], but this progression seems to be slower than in CIN 3 lesions. Some authors suggested that progression or persistence of VaIN are potentiated by multifocal lesions[10], ano-genital neoplasic syndrome[10], HR--HPV infection[11], grade 3 VaIN[11], imunossupression[10] and cigarette smoking[11].

The aims of the present study were to determine risk factors for the development and evolution of high-grade VaIN and to assess the effectiveness of treatment modalities, by analysing clinical features, management and outcomes in a sample of 23 patients.

POPULATION AND METHODS

A retrospective study was conducted at the Department of Gynecology comprising patients with diagnosis of high-grade VaIN (VaIN 2 or VaIN 3), managed between 1994 and 2012.

The following data were collected by reviewing individual case files: age, history of cigarette smoking, immunossupression related disease or medication, previous lower genital tract intraepithelial neoplasia, history of hysterectomy, methods of diagnosis, colposcopic findings, lesion location, HR-HPV infection, treatment options and outcomes.

The statistical analysis included descriptive statistics, with determination of means and standard deviations.

RESULTS

From 1994 to 2012, twenty-three patients presenting high-grade VaIN were managed at our department, fifteen of which had VaIN 3 (65%) and eight had VaIN 2 (35%).

The mean age at diagnosis was 57 ± 10 years, ranging from 40 to 74 years. From the 14 women inquired about smoking, only 2 (14%) were cigarette smokers. Four patients (17%) were potentially immunossupressed – two had diabetes mellitus, one had rheumatoid arthritis and one had multiple sclerosis. Seventeen women (74%) had previous hysterectomy. The indications for this procedure were cervical cancer or CIN 3 in 13 cases (76.5%), and uterine myomas in 4 cases (23.5%). The delay between the hysterectomy and diagnosis of VaIN was on average 12.7 years (ranging from 10 months to 33 years). This interval was shorter for women with previous CIN 3 / SCC compared with women surgically treated for benign disease (7.5 years *versus* 19.7 years, respectively). All 6 patients without previous hysterectomy had cervical neoplasia (67% CIN 3), synchronous in 4 patients and previous in 2 patients. Therefore, 19 of all studied patients (83%) had associated lower genital tract neoplasia.

VaIN was detected by cytological screening in 15 cases (65%), by colposcopy in 7 cases (30%) and by biopsy in 1 case (4%). All diagnosis of VaIN were confirmed by histologic examination. Distribution of abnormal cytological results by VaIN grading is presented in Table I. Testing for HR-HPV was performed in only 5 patients, 4 of which were positive.

Colposcopic findings were diverse, most frequently white epithelium (n=12), punctuation (n=9), mosaic (n=4) and atypical vessels (n=3). Only one case presented multifocal lesions. All patients presented lesions in the upper third of the vagina. One had extension to the medium third and other to the medium and lower thirds of the vaginal mucosae.

Treatment procedures and outcomes in each treatment group are listed in Table II. One patient abandoned follow-up, without any treatment, returning only 6 years later after development of vaginal SCC. Another patient didn't receive any treatment due to repeated missed appointments. Nevertheless, she had complete regression of lesions one year after diagnosis.

After treatment, follow-up was performed for a mean time of 35 months, ranging from 6 months to 10 years.

Relapse was detected in two patients treated by laser ablation, both after 36 months of follow-up. In three cases, there was progression to vaginal SCC. In one case, VaIN 3 was detected in a 62-year-old patient, with rheumatoid arthritis, 12 years after hysterectomy due to uterine myomas, with progression to vaginal micro-invasive SCC occurring 20 months after treatment by laser excision. In another case, a 74-year-old patient

TABLE I. CYTOLOGICAL ANOMALIES DISTRIBUTED BY VAIN GRADING

	LSIL	HSIL	SCC
	n	n	n
VaIN 2 (n=4)	3	-	1
VaIN 3 (n=11)	1	6	4
Total	4	6	5

VaIN – Vaginal intraepithelial neoplasia; LSIL – Low-grade squamous intraepithelial lesion; HSIL – High-grade squamous intraepithelial lesion; SCC – Squamous cell carcinoma

TABLE II. PATIENT OUTCOMES DISTRIBUTED BY TREATMENT OPTION

	Clearance n (%)	Persistence n (%)	Relapse n (%)	Progression n (%)
No treatment (n=2)*	1 (50)	–	–	1 (50)
Laser ablation (n=6)	3 (50)	1 (17)	2 (33)	-
Loop / laser excision (n=10)	7 (70)	1 (10)	–	2 (20)
Colpectomy (n=5)	3 (60)	2 (40)	–	–
Total treated (n=21)	13 (62)	4 (19)	2 (9,5)	2 (9,5)
Total (n=23)	14 (61)	4 (17)	2 (9)	3 (13)

* Missed appointments

TABLE III. RISK FACTORS AND OUTCOMES AFTER TREATMENT

	Clearance n (%)	Persistence n (%)	Relapse n (%)	Progression n (%)
Immunossupression (n=4)	2 (50)	–	1 (25)	1 (25)
Cigarette smoking (n=2)	2 (100)	–	–	–
HR-HPV + (n=4)	2 (50)	1 (25)	1 (25)	–
Current or past cervical neoplasia (n=17)	9 (53)	5 (29)	2 (12)	1 (6)
VaIN 2 (n=8)	4 (50)	1 (12,5)	2 (25)	1 (12,5)
VaIN 3 (n=13)	8 (61)	4 (31)	–	1 (8)

HR-HPV – High risk human papillomavirus; VaIN – Vaginal intraepithelial neoplasia

had diagnosis of VaIN 3 ten months after hysterectomy due to invasive cervical SCC; VaIN 3 progressed to invasive vaginal SCC and she died from this disease 8 months after diagnosis. A third patient, previously mentioned, was a 66-year-old woman diagnosed with VaIN 2 fourteen years after hysterectomy due to micro-invasive cervical SCC. She missed treatment and follow-up, returning only 6 years later after development of vaginal SCC. Patients with persistent disease, relapse or progression underwent further treatments.

Table III presents patient outcomes considering possible risks factors for persistence, relapse and progression.

COMMENTS

Historically, high grade VaIN is reported in older women than high grade CIN, with mean ages over 60 years[3,7], close to the mean age observed in our study (57 years). However, other authors have reported VaIN series with incidence peaks under 60 and even under 40 years-old[11-15].

In the current literature, smoking habits and immunossupression have been consistently linked to the development of lower genital tract neoplasia[3,6,9]. The incidence of smokers among women with VaIN reaches, in some studies, rates of 40 – 50%[9,12], an incidence much higher than in the present study (14%). However, not all patients were inquired about their smoking habits. In 17% of this sample, immunossupression may be related with the development of VaIN, in accordance with data found in literature[10].

In this sample, 74% had previous hysterectomy, 76.5% due to cervical neoplasia and 23.5% due to benign disease; these findings suggest a relation between hysterectomy and the development of VaIN, possibly stronger for hysterectomy after malignant disease but still relevant after benign disease, considering the much lower overall rate of hysterectomized women (1.2 to 5.6 per 1000)[16]. Indeed, there are reports in literature of VaIN developing in 5 to 18% of patients submitted to hysterectomy due to cervical neoplasia[2,17,18] and in 3.9% of patients that underwent this procedure due to benign disease[8] *versus* an overall incidence of 0.2 to 2 / 100.000 women per year[3]; *Murta* and colleagues re-

ported a history of hysterectomy in up to 69.6% of patients that develop VaIN, 87% of which underwent the surgery for treatment of cervical neoplasia and 8.6% for treatment of uterine myomas[12]. Although there is still some conflicting data about correlation between hysterectomy due to benign conditions and VaIN[3], *Frega* and colleagues presented data supporting that the incidence of VaIN in hysterectomized women following benign pathologies doesn't differ significantly from the malign group (3.9 *vs* 5.5%)[8]. The present analysis suggests a longer delay from hysterectomy to development of VaIN in the group of previous benign conditions than in the group of previous cervical neoplasia. *Ruiz-Moreno* and colleagues obtained similar findings, with an average of 9 years in the benign disease group and 2.4 years in the malign disease group[19].

In this study, none of the patients presented anal or vulvar neoplasia, but the rate of patients with previous or synchronous cervical neoplasia, either invasive or intraepithelial, was 83%, slightly higher than what is found in current literature (70%)[10,13].

Usually, VaIN is discovered through colposcopy performed for an abnormal Pap test result in post-hysterectomy cases or during evaluation for cervical disease[3]. Indeed, this situation occurred in 65% of the present sample. Distribution of cytologic anomalies by VaIN grading, presented in Table I, suggests a tendency for higher grade cytologic results in VaIN 3 than in VaIN 2. On the other hand, the colposcopic findings were apparently unrelated to the lesions grading.

VaIN is commonly observed in the upper third of the vagina or along the vaginal cuff suture line[4,6], with several authors reporting incidences of around 85 – 90% in this location[12,13]. In our study, 100% of the cases presented lesions in upper third of vagina. Curiously, only one patient presented multifocal neoplasia, in spite of VaIN being described in literature as often occurring as a multifocal lesion[4,7].

Patients were managed using one of three treatment options. Considering all treatments, a high rate of clearance (62%) and a low rate of progression (9,5%) were observed, which is consistent with various studies reporting great success rates with low progression rates. *Massad* reported clearance in 63.2% of cases and no cases of progression from 19 high-grade VaIN treated by ablation or excision[20]. Similarly, *Sillman* and colleagues reported 70.3% of clearance and 5.4% of progression to invasion in a sample of 74 VaIN patients that underwent various types of treatment, including 5-fluoruracil, not used in the present study[10].

Some authors have suggested excisional procedures to be more effective than ablation. *Dodge* and colleagues found higher relapse rates after laser treatment than after vaginectomy (38% *vs* 0%)[15]; *Lenehan* and colleagues reported an ablation failure rate of 41% compared to 16% for patients submitted to surgery[14]. In the present study, none of the adopted procedures showed apparent superiority. While excisional techniques resulted in a higher rate of clearance, there were two cases of progression among patients in this treatment group.

In spite of the limited size of the no-treatment group in this study, the observed progression rate of 50%, compared with a rate of 9.5% in the treatment group advises against expectant management in high grade VaIN. However, *Aho* and colleagues underwent a 3-years follow-up study of untreated VaIN, observing a high regression rate (78%), with 13% of persistence and 9% of progression to cancer[11].

Diverse risk factors for persistence, relapse or progression of VaIN have been proposed. Data presented in Table III suggest that VaIN grade (2 *vs* 3) and cigarette smoking aren't relevant risks factors. On the other hand, remaining risk factors - immunossupression, HR-HPV infection, associated cervical neoplasia – seem to have some influence in worse outcomes after treatment.

CONCLUSIONS

The present study's results suggest that previous hysterectomy due to both malign and benign conditions and past or current cervical neoplasia are important risk factors for development of high-grade VaIN, although the limited sample size and short follow-up periods don't allow for more definitive conclusions.

One case of progression, observed in the treated group, had a history of hysterectomy due to benign condition, which supports the maintenance of those women under vaginal cytologic screening. However, the overall low incidence of VaIN justifies current cytologic screening guideline.

Immunossupression, HR-HPV infection and associated cervical neoplasia seem to be relevant risk factors for poor outcomes.

None of the different treatment options appeared to be more effective than the others, although they seem to be preferable over expectant approach in high-grade VaIN management.

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