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Recurrence and risk of progression to lower genital tract malignancy in women with high grade VAIN

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HIGHLIGHTS

- VAIN is a rare disease that recurs without a clear prediction model
- Progression to carcinoma of the vagina is a rare but associated risk of VAIN
- Vaginal patency post treatment should be discussed during patient counseling

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ABSTRACT

Objective. High-grade vaginal intraepithelial neoplasia (VAIN) II–III has a variable clinical course. Due to the rarity of VAIN, existing data on the efficacy of treatment, risk of recurrence and progression to carcinoma is limited. Our objective was to evaluate predictors of recurrent disease and describe the risk of progression to carcinoma.

Methods. Under an IRB-approved protocol 42 patients with biopsy-proven VAIN II–III from 1995 to 2015 were retrospectively identified. Demographics, treatment, and clinical course were abstracted from medical records. Patients were followed with semi-annual colposcopy and biopsies at physician discretion. Standard statistical analyses were applied.

Results. Median patient age was 58 years old (range 20–81). Median follow-up time was 45 months (range 9–195). Management included excision (31%), laser ablation (33%), topical agents (19%), and observation (10%), with the following rates of recurrence: 38%, 43%, 75%, and 50% ($p = 0.26$). 20 patients (48%) had recurrent or persistent disease during treatment follow-up. No specific primary treatment was significantly more effective in preventing recurrence. Recurrence of VAIN II–III occurred at a median of 17.4 months (7–78 months) from time of initial diagnosis. Five (12%) patients developed invasive cancer of the lower genital tract. Median time to cancer diagnosis was 64 months (30 to 101 months).

Conclusions. Patients with VAIN II–III are at high risk of recurrence and progression, suggesting the need for ongoing evaluation with cytology and comprehensive colposcopy by a skilled specialist. There were no clear risk factors or histopathologic criteria which predicted recurrence or progression to cancer.

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1. Introduction

Vaginal intraepithelial neoplasia (VAIN) is an uncommon premalignant condition with a lack of long-term follow-up data to definitively guide patient care. In particular, high-grade VAIN has a variable clinical course and its natural progression to carcinoma has not been completely characterized. High-grade VAIN (VAIN II–III) has been reported to progress to invasive vaginal cancer in 2% to 12% of cases [1,2]. In the United States, approximately 3170 women are diagnosed annually with vaginal cancer with 880 attributable deaths [3].

Potential risk factors for development of VAIN include presence of HPV, prior pelvic radiation (usually after treatment for cervical cancer), history of vaginal condylomata, prior hysterectomy for cervical intraepithelial neoplasia (CIN), human immunodeficiency infection (HIV), and history of in utero exposure to diethylstilbestrol (DES) [4–6].

Due to the rarity of high-grade VAIN, existing data on the efficacy of treatment, risk of recurrence, and progression to vaginal carcinoma or other lower genital tract carcinoma is limited. It is important to elucidate the role of potential lower genital tract dysplasia field effect and the subsequent risk of malignancies in women with high-grade VAIN. The elucidation of risk factors associated with recurrence and

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progression of vaginal dysplasia are needed to inform optimal treatment and surveillance for patients with high-grade VAIN. In this study we evaluate predictors of disease recurrence and describe the risk of progression to lower genital tract carcinoma in a cohort of women with high-grade VAIN.

2. Materials and methods

Under an IRB-approved protocol we identified patients with biopsy-proven VAIN II–III who underwent treatment and/or surveillance between January 1995 and May 2015 at Cedars-Sinai Medical Center in Los Angeles, California. Ten patients with VAIN II and 32 patients with VAIN III were identified. If a patient had a range of VAIN severity on biopsy at initial diagnosis, the highest grade of VAIN was listed as the final pathologic diagnosis. Patients with a history of vaginal cancer and those without a biopsy-proven diagnosis of VAIN II–III were excluded from the study. No patient had a history of prior vaginal or pelvic radiation. Demographics, treatment, and clinical course were documented.

Patients were followed with semi-annual colposcopy, cytology and biopsies at the discretion of the provider. With the exception of one patient who was followed by an experienced senior gynecologist, all patients were treated and managed by gynecologic oncologists. Patients were followed until death, completion of study time period, or loss to follow-up. The following data was abstracted: location of disease, margin status if treated with excision, smoking history, prior hysterectomy, history of cervical dysplasia and/or cervical cancer, diethylstilbestrol (DES) exposure, evidence of HPV infection based upon cytologic or histologic evidence of HPV related changes), initial treatment modality, recurrence status, progression to cancer, and evidence of immunosuppression (patients with HIV, autoimmune disease, and/or transplant requiring active use of immune modulating medications). High-risk HPV subtype testing with DNA was not performed. Treatment types were categorized as observation, topical management (i.e. fluorouracil), surgical excision (vaginectomy or local excision), and ablative procedures (i.e. laser). Patients who received more than one concurrent primary treatment (n = 2) were excluded from analysis evaluating efficacy of treatment.

The primary outcome measures were recurrence of high-grade VAIN and progression to carcinoma. Patients were categorized as having persistent disease if repeat vaginal biopsy confirmed the same or higher histologic grade of VAIN. Patients were considered to have recurrent disease when there was resolution of VAIN by exam, vaginal pap smear, or biopsy following primary treatment with subsequent biopsy-confirmed high-grade VAIN or lower genital tract cancer (vaginal, vulvar, or anorectal). Categorical differences in clinical and histopathologic factors between patients were examined with Chi-squared and Fisher's exact tests while continuous variables were examined with the Mann-Whitney *U* test. A two-tailed p-value of 0.05 was considered to be statistically significant. Statistical analysis was performed with GraphPad Prism (version 5.0 for Windows; GraphPad Software, San Diego, CA).

3. Results

Forty two patients met criteria for inclusion in this study: 10 had VAIN II and 32 had VAIN III. Median age of the entire cohort was 58 years old (range 20–81) and the majority of patients were Caucasian (73%). Median follow-up time was 72 months (range 9–240). Ninety-seven percent of women with high grade VAIN and available data had HPV-related changes present on histology or cytology and 90% of women had a prior history of CIN. Eighteen patients (43%) had a prior hysterectomy due to cervical intraepithelial neoplasia (n = 15) or early stage cervical cancer (n = 3). Twelve patients (29%) had a prior hysterectomy for other indications including 2 women (5%) in the setting of endometrial cancer and 4 women (10%) due to benign indications. Among all patients with a known hysterectomy date prior to development of VAIN, the median interval between hysterectomy and VAIN diagnosis was 35 months (range 0–541). Ten women (24%) had a history of prior smoking and one active smoker at the time of high-grade VAIN diagnosis and 24% had never smoked. Three patients (7%) were immunosuppressed: one status post a renal transplant, one with systemic lupus erythematosus, and one with HIV. Of note, during follow up visits routine documentation of vaginal patency was not reported.

Twenty women (48%) had recurrent high grade VAIN. Table 1 compares demographic and histopathologic characteristics of patients by recurrence status. Median follow-up time was longer for those patients with recurrence/persistence (80 months, range 22–240 months) than those without (59 months, range 9–149 months), p-value 0.034. HPV infection, a prior history of cervical intraepithelial neoplasia (CIN), prior hysterectomy, smoking history, immunosuppression), and DES exposure did not affect the risk of recurrence. Margin status, VAIN II versus VAIN III, nor multifocal lesions predicted recurrent disease. Initial treatment for women with high grade VAIN consisted of surgical excision in 13 (31%), ablation in 14 women (33%), topical therapy in 8 (19%), and combination therapy in 2 (5%). Four women were observed and one patient had unknown therapy. The risk of recurrence was comparable between all treatment modalities. Recurrence rates for each treatment modality were: surgical excision 38%, ablation 43%, topical therapy 75%, and observation 50% (p = 0.4).

Recurrent disease occurred at a median of 17.4 months (range 7–78) from the time of initial diagnosis. 20 patients (48%), 4 women with VAIN II and 16 women with VAIN III, had recurrent or persistent disease. Of these 20 patients, 3 progressed to invasive vaginal or vulvar cancer, and 1 developed both vaginal and anal cancer. An additional patient,

Table 1
Demographic and histopathologic characteristics of women with VAIN II–III.

	Patients without recurrence/persistence (n = 22)	Patients with recurrence/persistence (n = 20)	P-value
Age at Dx (median, range)	58 (20–81)	59 (28–77)	0.90
Follow-up (median, range)	42 (9–130)	65 (22–195)	0.034
HPV present on biopsy/cytology*	16 (94%)	18 (100%)	0.49
History of CIN*	18 (90%)	17 (89%)	0.61
Prior hysterectomy	14 (64%)	16 (80%)	0.31
Ever smoked	4 (18%)	6 (30%)	0.47
Immunosuppression	2 (9%)	1 (5%)	1.0
Multifocal lesion*	10 (56%)	6 (46%)	0.72
DES exposure	0 (0%)	3 (15%)	0.1
*Initial management**			
Surgical treatment	8 (40%)	5 (26%)	0.40
Laser ablative Treatment	8 (40%)	6 (32%)	
Topical treatment	2 (10%)	6 (32%)	
Observation	2 (10%)	2 (10%)	

* Data not available for all patients.