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The diagnostic challenge of vulvar squamous cell carcinoma: Clinical manifestations and unusual human papillomavirus types

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To the Editor

Treatment for early stage vulvar cancer lesions is readily available with limited morbidity; advanced stages of the disease, however, require interventions with serious morbidity. We sought to characterize clinical presentation of vulvar carcinoma to better understand reasons for delayed diagnosis and to determine which human papillomavirus (HPV) subtypes are causative.

Twenty-three cases of invasive vulvar squamous cell carcinoma (SCC) were identified using the pathology databases at the University of Pennsylvania. DNA was extracted from formalin-fixed paraffin embedded samples. HPV-PCR products were detected with PGMY-GP+-primer system. HPV-PCR products were then cloned and sequenced. NCBI-BLAST analysis revealed the presence of different HPV types.¹ Clinical data were extracted from the medical record (Table I).

Studies have shown that vulvar cancer patients often have lengthy medical contact and treatment for vulvar symptoms prior to diagnosis.^{2,3} Most patients in our study (74%) were aware of vulvar symptoms (itching, bleeding, discharge), lesions, or both. Documented exam descriptors used for the vulvar cancers included “exophytic,” “plaque,” “fungating,” “white,” “raised,” “thickened,” and “erythematous.” With these variable presentations, vulvar cancer can mimic conditions including lichen sclerosus, contact dermatitis, warts, and other inflammatory or benign neoplastic conditions. The mean time from initial presentation to biopsy revealing invasive SCC was 3.6 months. Prior studies show delays from 6 months to 5 years between first reported symptoms and diagnosis.² Our findings highlight the need

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for providers to maintain a low threshold for biopsy to rule out malignant disease in any long-standing vulvar lesion or “rash.”

Clinicians should also be aware of the 2 pathways for development of vulvar SCC. The first is HPV-induced, “usual type” vulvar SCC, which occurs in younger women. Two thirds (68.8%) of invasive vulvar cancers diagnosed are usual-type caused by HPV.³ The second pathway occurs predominantly in older patients, independent of HPV infection, often in association with chronic inflammation of the vulva (including lichen sclerosus).⁴

Usual type vulvar SCC is caused by high-risk HPV types such as 16, 18, and 33. In our study, 75% of cases were HPV positive. We noted a greater likelihood of HPV positivity among past and current smokers ($P < .10$) (Table II). The most common subtype was HPV 16 (8 samples). HPV 18, 45, and 53 were each detected in one sample. Two samples tested positive for HPV 120, a recently characterized novel β -PV related most closely to HPV-23.⁵ The finding of HPV 120 in 3 vulvar cancer specimens is intriguing as it is a relatively newly described HPV genotype. HPV 120 has been described to have multiple anatomic niches, including oral, vulvar, penile, and anal mucosa. However, the pathologic consequences of HPV 120 infection remain unclear.⁵

Vulvar SCC can have varied clinical presentations leading to significant diagnostic delay. Providers should include carcinoma in their differential of vulvar dermatoses and maintain a low threshold for conducting biopsy. In our study, 76% of samples were positive for high-risk HPV, some with unusual subtypes (eg, HPV 120), suggesting that currently available vaccines may not entirely eliminate the risk for vulvar cancers.

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Table I
Demographic and lesion characteristics

Age at diagnosis (median, IQR)	61	(43-76)
Smoking status (n, %)		
Never smoker	8	35%
Past smoker	6	26%
Current smoker	7	31%
Smoking status unknown	2	9%
Medical history (n, %)		
History of HIV infection	3	21%
History of genital warts	6	27%
History of diabetes	5	22%
History of inflammatory bowel disease	0	0%
History of organ transplant	2	9%
History of other cancer	4	17%
History of autoimmune disease	0	0%
History of eczema	1	4%
History of prior systemic treatments (n, %)		
Yes	3	14%
None/unknown	20	86%
History of topical treatments to vulvar area (n, %)		
Yes	8	35%
None/unknown	15	65%
History of abnormal Paps (n, %)		
Yes	8	35%
None/unknown	15	65%
History of concurrent or previous vulvar dermatoses diagnosed clinically (n, %)		
Yes	4	83%
None/unknown	19	17%
Previous vulvar symptoms (n, %)		
Yes	17	74%
None/unknown	6	26%
Lesion size in cm (median, IQR)*		
Type of provider who first evaluated patient (N)		
Ob/gyn	18	78%
Other	5	22%
Time from initial presentation in medical system to biopsy in months (Median, IQR) [†]	1	(0-2)

IQR, Interquartile range.

* Data available for 15 of 23 specimens.

[†] One day to 1 month rounded up to 1 month.

Table II
Associations with HPV type

Demographic characteristic	HPV type		P-value
	Positive	Negative	
	N = 13	N = 4	
Age at diagnosis (median)*	59	67	.428
Past or current smoker	10	1	.099
History of genital warts	4	0	.529
History of immunosuppression [†]	6	2	1
History of prior systemic treatments	2	1	1
History of topical treatments to vulvar area	5	1	1
History of abnormal Pap smear	4	1	1
History of concurrent or previous vulvar dermatoses diagnosed clinically	3	1	1
Previous vulvar symptoms	10	2	.538
Lesion size in cm (median)*	1.5	1.65	.831
Time from initial presentation in medical system to biopsy in months (median)*	1	2	.64

P-values for Fisher exact test unless otherwise noted.

* Kruskal-Wallis equality of populations rank test. DNA quality assessment by beta-globin reference gene PCR of the DNAs extracted from the sections. Six samples were negative and were excluded from the HPV testing, leaving 17 total cases reported.

[†] Patients with a known history of diabetes mellitus, organ transplant, or HIV.