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Case series

Paget's disease of the vulva: A review of 89 cases☆

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ABSTRACT

The purpose of this study was to retrospectively review the clinical characteristics and outcomes of a series of women with Paget's disease of the vulva. A retrospective review was performed of 89 women with Paget's disease of the vulva evaluated at a single institution between 1966 and 2010. Medical records were reviewed for demographic information, clinical data, pathologic findings, treatment modalities and outcomes. We found that the primary treatment was surgery for 74 (83.1%) patients, with positive margins noted in 70.1% of cases. Five patients (5.6%) underwent topical treatment with imiquimod and/or 5-fluorouracil, one patient (1.1%) underwent laser ablation and treatment was unknown in 9 patients (10.1%). The majority of patients had multiple recurrences, with 18% having four or more recurrences. There were no significant differences in recurrence rates between patients who underwent surgery and those who did not. Furthermore, there was no association between positive margins following primary surgery and recurrence. Forty-one patients (46.1%) were diagnosed with 53 synchronous or metachronous cancers. Seven patients (7.9%) were found to have invasive vulvar cancer with 1 mm or more depth of invasion, but none of the patients died of Paget's disease or associated vulvar/vaginal cancer. Our findings suggest that the majority of patients with Paget's disease of the vulva develop multiple recurrences regardless of treatment modality or margin status. Alternatives to surgery are needed to better care for women with this disease.

1. Introduction

Paget's disease of the vulva is a rare vulvar neoplasm most commonly seen in postmenopausal women. Mammary Paget's disease involving the nipple and areola was first described by Sir James Paget in 1874 (Paget, 1874). Subsequently in 1889, Dr. Crocker reported the first case of extramammary Paget's disease affecting the scrotum and penis (Crocker, 1889). Paget's disease of the vulva was first reported in 1901 by Dr. Dubreuilth (Dubreuilh, 1901).

Paget's disease of the vulva usually presents as a pink eczematous lesion with white islands of hyperkeratosis accompanied by pruritus. Pathologically it resembles mammary Paget's of the nipple and areola. It is a disease more often diagnosed in Caucasian, postmenopausal women (Kay and Southwood, 1964; Tebes et al., 2002; Black et al., 2007). Patients with Paget's disease of the vulva are at risk for a second synchronous or metachronous neoplasm: colorectal adenocarcinoma, cervical adenocarcinoma, carcinoma of the transitional epithelium from the renal pelvis to urethra, breast and vulvar carcinoma (Preti et al., 2000; Onaiwu et al., 2014). Routine screening with colonoscopy, Pap test, mamogram and cystoscopy is therefore recommended (Tebes et al., 2002; Feuer et al., 1990).

Paget's disease of the vulva is often limited to the epidermis and mucosa without invasion. The optimal management of Paget's disease of the vulva remains unclear. Surgical excision is usually the primary therapy (Edey et al., 2013). Furthermore, the lesions often extend past clinically apparent borders resulting in positive margins, and surgical excision is limited by the anatomy of the vulva. In addition, the disease is often multifocal and many patients require multiple excisions resulting in significant morbidity. Alternative treatment strategies are

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therefore needed. The objective of our study was to determine prognostic factors, risk factors for recurrence, associated malignancies, and outcomes of some treatment methods for Paget's disease of the vulva.

2. Methods

We performed a retrospective chart review of 89 patients with Paget's disease of the vulva evaluated at the University of Texas MD Anderson Cancer Center between 1966 and 2010. Institutional Review Board approval was obtained with a waiver of informed consent. Medical records were reviewed for demographic information, clinical data, pathologic findings, treatment modalities, and outcomes. Eligible patients were identified using databases from the Departments of Gynecologic Oncology and Pathology. Pathologic diagnosis of Paget's disease of the vulva for all patients was confirmed by a Gynecologic Pathologist at the University of Texas MD Anderson Cancer Center. Invasive Paget's disease was defined as disease extending beyond the basement membrane. Invasive cancer was defined as ≥1 mm of invasion.

A positive margin was defined as Paget's cells within 1 mm of the surgical margin. Residual disease was defined as Paget's cells found in the pathology specimen of the subsequent procedure is performed within three months of the prior procedure. If the subsequent procedure was performed after three months, this was considered recurrent disease. The follow-up period was defined as the time between initial Paget's disease diagnosis and the date of last contact.

Descriptive statistics were used to summarize the patient demographic and clinical characteristics. Fisher's exact test was used to compare patients with recurrence to those without recurrence with respect to types of primary treatment received and margin status among those patients with primary surgery. Study data were collected and managed using REDCap electronic data capture tools hosted at MD Anderson (Harris et al., 2009). REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies.

3. Results

Eighty-nine patients were identified that met inclusion criteria for the study. The median age at diagnosis was 67 years (range: 32–89 years). The majority of patients were Caucasian ($n = 83$, 93.3%). The median duration of symptoms prior to diagnosis was 10 months (range: 1–204 months). The main presenting symptom was pruritus ($n = 43$, 48.3%).

Primary treatment consisted of surgery for 74 (83.1%) patients including wide local excision ($n = 55$, 61.8%), radical vulvectomy ($n = 13$, 14.6%), skinning vulvectomy ($n = 4$, 4.5%), and Mohs surgery ($n = 2$, 2.3%). Margin status was available for 54 (73.0%) of the 74 patients who had surgery as primary treatment. Of these 54 patients, 47 (87.0%) were found to have positive margins. Five (5.6%) patients underwent topical treatment as primary therapy with imiquimod ($n = 4$, 4.5%) or 5-fluorouracil ($n = 1$, 1.1%). One (1.1%) patient underwent laser ablation (Table 1).

Table 1
Primary treatment ($n = 89$).

Primary treatment	N (%)
Surgery:	74 (83.1%)
Wide local excision	55 (61.8%)
Radical vulvectomy	13 (14.6%)
Skinning vulvectomy	4 (4.5%)
Mohs surgery	2 (2.3%)
Topical therapy:	5 (5.6%)
Imiquimod	4 (4.5%)
5-Fluorouracil	1 (1.1%)
Laser ablation	1 (1.1%)
Unknown	9 (10.1%)

Table 2
Recurrent disease ($n = 89$).

Number of recurrences	N (%)
0	37 (41.6%)
1	20 (22.5%)
2	11 (12.4%)
3	5 (5.6%)
4	7 (7.9%)
5	5 (5.6%)
6	0 (0.0%)
7	1 (1.1%)
8	2 (2.2%)
9	0 (0.0%)
10	1 (1.1%)

Fifty-two (58.4%) patients developed recurrent disease following primary treatment (Table 2). The majority of patients had multiple recurrences, with 18.0% of patients having four or more recurrences, including one patient who was treated for 10 recurrences (Onaiwu et al., 2014). The most common treatment for recurrent disease was surgery with 38 of the 52 patients (73.1%) undergoing one or more procedures, 21 (40.4%) patients underwent two or more surgical procedures, and 10 (19.2%) underwent three or more surgical procedures. Topical therapies with imiquimod and/or 5-fluorouracil were also used for recurrent disease in 23 (44.2%) patients.

Recurrence rates were compared by primary treatment modality (Table 3). There were no significant differences in recurrence rates in patients who underwent surgery and those who did not. There also were no significant differences by type of surgery. There also was no association between positive margin status at time of primary surgery and recurrence, with 26/47 (55.3%) with positive margins developing recurrent disease compared with 4/7 patients (57.1%) with negative margins developing recurrent disease ($p = 0.9999$). Seven (7.9%) patients were diagnosed with invasive vulvar/vaginal cancer with 1.0 mm or more depth of invasion (Table 4).

Forty-one of the 89 patients (46.1%) with Paget's disease were diagnosed with 53 synchronous (92.7%) or metachronous (7.3%) cancers. Of those with metachronous cancers, the time between Paget's diagnosis and cancer diagnosis ranged from 2 weeks to 19 years. The most common types included breast ($n = 13$, 14.6%), bladder ($n = 6$, 6.7%), colorectal ($n = 5$, 5.6%), and endometrial ($n = 4$, 4.5%). Follow-up data were available for 81 patients, with a median follow-up of 6.1 years (range 0–34.1). At date of last contact, 19 (23.5%) patients were alive without evidence of disease, 25 (30.9%) were alive with active Paget's disease, and 45 (55.6%) have died of other causes. None of the patients in our study died of Paget's disease or associated vulvar cancer.

Table 3
Recurrence rates by treatment modality.

	No recurrence ($N = 37$)	Recurrence ($N = 52$)	p-Value
Primary surgery ($n = 74$):	28 (37.8%)	46 (62.2%)	NS
Wide local excision ($n = 55$)	19 (34.5%)	36 (65.5%)	
Radical vulvectomy ($n = 13$)	7 (53.8%)	6 (46.2%)	
Skinning vulvectomy ($n = 4$)	2 (50.0%)	2 (50.0%)	
Mohs surgery ($n = 2$)	0 (0.0%)	2 (100.0%)	
Margin status ($n = 74$):			NS
Positive margins ($n = 47$)	21 (44.7%)	26 (55.3%)	
Negative margins ($n = 7$)	3 (42.9%)	4 (57.1%)	
Unknown margin status ($n = 20$)	4 (20.0%)	16 (80.0%)	
Topical therapy ($n = 5$):	1 (20.0%)	4 (80.0%)	NS
Imiquimod ($n = 4$)	1 (25.0%)	3 (75.0%)	
5-Fluorouracil ($n = 1$)	0 (0.0%)	1 (100.0%)	
Laser ablation ($n = 1$)	0 (0.0%)	1 (100.0%)	NS
Unknown ($n = 9$)	8 (88.9%)	1 (11.1%)	NS