

Clinicopathologic analysis of extramammary Paget's disease

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Summary

Purpose: To retrospectively analyze the clinicopathologic characteristics of patients with extramammary Paget's disease who were surgically treated in a single institution. **Method:** The charts of 14 patients with extramammary Paget's disease were retrospectively reviewed, and the clinicopathologic data were collected and analyzed. **Results:** From January 1990 to July 2009, 14 patients were treated at our institution. Most patients (11/14 patients) had delayed diagnosis. Two patients (14.3%) had associated malignant neoplasms. Eight of 14 patients (57.1%) had positive surgical margins; of these patients, five patients had no evidence of recurrence. In the six patients with negative surgical margins, two patients (33.3%) developed recurrence. **Conclusions:** The diagnosis of extramammary Paget's disease is commonly delayed. Because of the possible association with other malignancies before or after the diagnosis of extramammary Paget's disease, thorough examinations are recommended. Disease recurrence is common regardless of the surgical margin status, so long-term monitoring of patients is recommended.

Key words: Extramammary Paget's disease; Retrospective; Clinicopathologic analysis.

Introduction

Sir James Paget described a nipple skin lesion associated with invasive ductal carcinoma of the breast in 1874 [1]; similarly, skin lesions on the vulva were first described by Dubrenilh in 1901 [2]. Extramammary Paget's disease (EMPD) occurs mainly among elderly, postmenopausal women and is a rare (1%-2%) neoplastic vulvar lesion [3, 4]. Clinically, EMPD is most commonly accompanied by pruritus (70%) [5, 6]. Due to the non-specific clinical presentation, such as a pink, eczematoid area with hyperkeratosis, these lesions are often mistaken for eczema or contact dermatitis, so the diagnosis and treatment are often delayed [5]. Because the tumor cells generally spread *in situ* in the epidermis, surgical excision is the standard treatment; however, the tumor usually extends well beyond the gross lesion based on histopathologic examination, and recurrence is common (21%-61%) [6, 9]. Thus, extensive resection with a sufficient tumor-free surgical margin is needed [10, 13]. Also, because there is an associated underlying skin or visceral adenocarcinoma in 20%-55% of cases, thorough examinations to identify other regional rectal, urothelial, or vulvar malignancies has been recommended at the time of diagnosis [7, 9, 12-16].

Because EMPD is such a rare condition, it has not been possible to estimate the true incidence or frequency with which it becomes clinically malignant or co-exists with a visceral adenocarcinoma. In addition, the clinical importance of positive surgical margins is unclear. The aim of this study was to retrospectively analyze the clinicopathologic characteristics of patients with EMPD who were surgically treated in a single institution.

Materials and Methods

After obtaining approval from our Institutional Review Board (IRB), our medical database was reviewed to identify all women with EMPD. Fourteen women who were surgically treated in the Division of Gynecologic Oncology at our institution between January 1990 and July 2009 were identified. The charts of these patients were retrospectively reviewed, and the data were collected regarding patient demographics, previous treatment, symptoms, disease location, surgical margin status, depth of invasion, associated malignancies, and status of recurrence. Disease recurrence was defined as a new lesion in a period > 6 months after surgery. Duration of follow-up was calculated as a period from pathologic diagnosis to the last visit. The relationship between microscopic margin status and disease recurrence was investigated.

Results

Fourteen patients with EMPD of the vulva were treated at our institution during the study period. The mean age of the patients was 54.3 years (range 29-72 years). The mean gravidity of the patients was 2.57 (range, 0-6). The topography of the lesion was the right labium [4], left labium [6], and bilateral labia [4]. The most common symptom at the time of diagnosis was vulvar pruritus (7/14 patients). Except for three patients who were asymptomatic and diagnosed incidentally, most patients (11/14 patients) had a delay from initial symptoms to pathologic diagnosis for a long time, with a median delay in diagnosis of 61.8 months (range, 4 months to 10 years). Two patients (14.3%) were treated with unilateral vulvectomy, five patients (35.7%) had wide local excisions (WLEs), and seven patients (50%) underwent radical vulvotomies. Also, except for four patients with primary repairs, ten patients underwent reconstructive procedures by a plastic surgeon (skin graft [1], fasciocutaneous flap [8], and gracilis myocutaneous flap [1]). Two patients (14.3%) had associations with malignant neoplasms; one

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Table 1. — Characteristics of patients with EMPD.

Patient's ID	Age	Gravidity	Symptoms	Location	Size (cm)	Duration of symptoms (months)	Underlying
1	58	3	pruritus	Lt. vulvar	10*5	60	not checked
2	71	4	vulvar mass	Lt. vulvar	2*2	72	none
3	71	2	pruritus	Rt. vulvar	5*4	60	none
4	68	6	pruritus	Rt. vulvar Periurethral	3*5	120	none
5	52	2	erythema	Lt. vulvar	4.5*5	0	none
6	42	2	vulvar mass	Rt. vulvar	0.5*0.5	4	none
7	67	3	erythema	Periurethral Perianal	6*5	0	recurrent breast ca.
8	45	1	pruritus	Periurethral Perianal	12*7	84	none
9	48	3	ulceration	Rt. vulvar	2.5*3	72	none
10	72	6	pruritus	Periurethral Perianal	7*7	120	none
11	57	2	pruritus	Rt. vulvar	10*4	4	none
12	52	2	pruritus	Lt. vulvar	3.5*4	60	none
13	29	0	none	Lt. perianal	3.5*3	0	none
14	29	0	bleeding	Lt. vulvar	10*7	24	vulvar adenoca

Table 2. — Clinicopathologic features of patients with EMPD.

Characteristics	No. of patients (%)
<i>Mode of treatment</i>	
unilateral vulvectomy ± reconstruction	2 (14.3%)
wide local excision ± reconstruction	5 (35.7%)
radical vulvectomy + reconstruction	7 (50.0%)
<i>Depth of invasion</i>	
CIS	13 (92.8%)
invasive to subcutaneous tissue	1 (7.2%)
<i>Margin status</i>	
positive	8 (57.1%)
negative	6 (42.9%)
<i>Adjuvant treatment</i>	
radiation	2 (14.3%)
none	12 (85.7%)
<i>Status of recurrence</i>	
yes	2 (14.3%)
no	12 (85.7%)

CIS: carcinoma *in situ*.

Table 3. — Treatment outcomes of EMPD by surgical margin status.

Margin status (Number of patients/%)	no recurrence	recurrence
Positive (8/57.1%)	8	0
Negative (6/42.9%)	4	2

patient had invasive vulvar adenocarcinoma, and one patient who had a history of breast cancer and underwent surgery > 10 years earlier was diagnosed with recurrent breast cancer during the 6-month follow-up period. Most patients (13/14 patients [92.8%]) had Paget cells confined to the epidermis; one patient had Paget cells infiltrating into the subcutaneous tissue with inguinofemoral lymph node metastasis and underwent postoperative adjuvant radiation treatment. The patient with underlying vulvar adenocarcinoma also underwent inguinofemoral lymph node dissection and postoperative adjuvant radiation treatment. Eight of 14 patients (57.1%) had positive surgical margins; of these patients, five patients who were followed regularly until recently had no evidence of recurrence after a median follow-up of 43 months. Of the six patients with negative surgical margins, two (33.3%) developed recurrences and received radiation treatment.

Discussion

EMPD is a rare disease which primarily affects elderly, postmenopausal women. Although we identified two cases involving 29-year-old patients, 11 of the other 12 patients were postmenopausal, with mean age of 58.6 years. Of note, our patients had a delay from initial symptoms to pathologic diagnosis of EMPD because of the non-specificity of their symptoms. Except for three patients who were asymptomatic and diagnosed incidentally, most patients (11/14) had delayed diagnosis for a long time, with a median of 61.8 months (range, 4 months to 10 years). Most patients had a history of using topical corticosteroids for the treatment of pruritus. Late diagnosis also occurred because many patients preferred not to visit a gynecologist due to personal taboos or a fear of malignancy [14].

Skin biopsy should be performed on all patients with pruritic eczematous lesions of apocrine gland-bearing areas that have failed to respond to standard topical treatment [13]. The differential diagnosis should include contact dermatitis, psoriasis, fungal infections, seborrheic dermatitis, lichen sclerosis, anogenital intraepithelial neoplasia, melanoma, histiocytosis, and mycosis fungoides [17]. Based on histopathologic examination, Paget's cells are large round cells with abundant pale cytoplasm and large vesicular nuclei, which may be central or laterally compressed. Mitotic figures are unusual. The lesions may be distributed singly or in groups within the epidermis and epithelia of adnexal structures [13]. Immunohistochemistry has been used to diagnose Paget's disease and to identify the likely cell of origin. Paget's cells typically stain for markers of apocrine and eccrine derivation, including low molecular weight cytokeratin (CK), gross cystic disease fluid protein (GCDFP-15), periodic acid-Schiff (PAS), and carcinoembryonic antigen (CEA); staining for S100 is negative [13].

Several studies have reported a high frequency (20%-55%) of associated underlying skin or visceral adenocarcinomas [7, 9, 12-16, 18-21]; more than 14.3% occurred in our study. Taking into consideration that EMPD occurs in elderly and postmenopausal women, patients with EMPD have an increased risk of developing a second malignancy [5]. Thorough examinations to detect other

regional rectal, urothelial, or vulvar malignancies are recommended at the time diagnosis of EMPD; appropriate diagnostic studies include the following: pelvic ultrasound, hysteroscopy, laparoscopy, and/or an MRI scan of the pelvis; colonoscopy, sigmoidoscopy and/or barium enema; cystoscopy and IVP; and mammogram and chest X-ray [13].

The standard treatment for EMPD is surgical excision. Traditionally, radical vulvectomy has been done because of the high recurrence rate and the risk of an underlying adenocarcinoma. However, this type of surgery is associated with significant disfigurement and a persistent local recurrence rate due to the characteristics of EMPD, such as multicentricity and ill-defined margins [6, 7-9, 15, 22, 23]. Therefore, many gynecologists advocate WLE of the visible lesion with resection to the fascia and a 2-3 cm grossly normal skin margin is adequate. In the current study, two patients (14.3%) were treated with unilateral vulvectomies, five patients (35.7%) had WLEs, and seven patients (50%) underwent radical vulvectomies with or without reconstructive procedures by a plastic surgeon. A high proportion of the radical vulvectomies in the current study may have been associated with the topography of the disease, the size of the lesion, and the fear of recurrence.

Some investigators have reported a reduction in local disease recurrence by up to 50% following surgical excision of vulvar EMPD with the use of intraoperative frozen section analysis [24], while others have reported that frozen resection analysis of surgical margins can be misleading in EMPD with false negative rates of 35% [25]. Indeed, permanent margin status is not predictive of local recurrence [6, 12, 25]. Although we did not use frozen section analysis in our study, the patients with positive surgical margins have had no evidence of local recurrence until recently after a median follow-up of 43 months. In the patients with negative surgical margins, two patients (33.3%) developed recurrences at 33 and 67 months post-operatively. These data suggest that patients with EMPD require long-term follow-up and careful examination of any suspicious vulvar lesions.

A limitation of our study was that number of patients was small due to the rarity of the disease. However, our report has highlighted the current state of clinicopathology, management, and prognosis of EMPD. The therapeutic strategies offering both a low rate of recurrence and minimal tissue destruction requires further investigation.

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