

Paget Disease of The Vulva: Report 5 Cases and Literature Review

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ABSTRACT

Vulvar Paget's disease is rare among patients with vulvar cancer. Commonly, this disease is presented in the vulva and seen in postmenopausal women. In this study, we reported five cases of vulvar Paget's disease referred to Bahman Hospital, Tehran, Iran, from 2013 to 2019.

The median age of patients diagnosed with Paget's vulvar disease was 56.2 years (ranges from 52 to 62 years); the oncology history of patients was negative. All patients underwent surgery, including wide local excision, hemivulvectomy, and bilateral vulvectomy. Invasive disease was observed in three patients. Surgical margins in three patients were involved by Paget's disease, and one recurrence (25%) was observed. Paget's disease should be diagnosed and treated by surgery as soon as possible to avoid worsening the prognosis of patients and recurrence.

Keywords: Paget's disease, Vulvar Paget's disease, Vulvar neoplasms, Vulvectomy



Introduction

Extramammary Paget's disease (EMPD) is a rare intraepithelial malignancy affecting apocrine glands, most commonly in the vulva and perianal regions (1), which is more prevalent in postmenopausal women (2). Vulvar Paget's disease typically presents as a pink eczematous lesion with pruritus accompanied by white islands of hyperkeratosis (3).

Pathologically, it resembles the nipple and areola of the mammary Paget's disease. Vulvar Paget's disease is diagnosed more often in postmenopausal women (4, 5). Patients with vulvar Paget's disease are at risk for a second synchronous neoplasm: cervical, breast, vulvar, or colorectal adenocarcinoma, carcinoma of the transitional epithelium from the renal pelvis to urethra (6). In these patients, routine screenings, such as colonoscopy, Pap smear test, mammogram, and cystoscopy, are recommended (7). Vulvar Paget's disease is often limited to the epidermis and mucosa without invasion (8).

Invasive vulvar Paget's disease accounts for <1% of all vulvar malignancies (9). To date, the best management of vulvar Paget's disease has remained

unclear. Surgical wide local excision with lateral margins extending from 2 to 3 cm beyond the clinically affected area is usually the primary therapy (8). In addition, the lesions often extend past clinically apparent borders resulting in positive margins, and the anatomy of the vulva limits surgical excision (4). In addition, the disease is often multifocal chronic with irregular histological margins that often extend beyond the visible margins of the lesions (10). The recurrence rates after wide local excision was reported 33%-60% (11).

In this study, we reported our experience of treating five patients with vulvar Paget's disease in Tehran, Iran

Case Report

Case 1

A 60-year-old postmenopausal woman, gravida 3, para 3, with a history of hypertension (HTN), vulvar itching, and irritation in the past two years (received

various medical treatments without any success) was referred to our institution because of her growing lesion. Physical examination revealed a large red and white eczematoid lesion in the vulva bilaterally ([Figure 1](#)). No abnormal cells were found in the cervix during the colposcopy. Preoperative punch biopsy confirmed Paget's disease. Abdominopelvic magnetic resonance imaging (MRI) before surgery were normal. Pap smear results and human papillomavirus (HPV) testing were normal.

Bilateral vulvectomy was done. The pathology report revealed bilateral vulvar Paget's disease without stromal invasion ([Figure 2](#)). Surgical margins were free. During her six month's post-operative follow-up, she had no evidence of any recurrences till today.



Figure 1. Large red and white eczematoid lesion in the vulva bilaterally

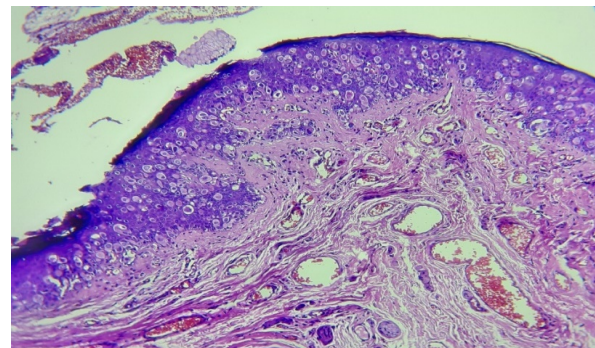
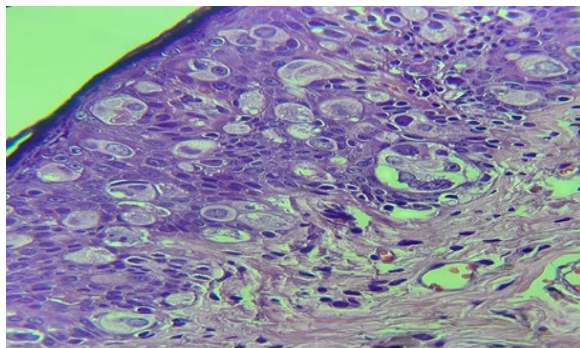


Figure 2. Single clusters of large cells with pale, vacuolated cytoplasm (Paget's cells) in the basal and above basal layer of the epidermis with cleft-like spaces between Paget's cells and neighboring keratinocytes

Case 2

A 50-year-old postmenopausal woman, gravida 3, para 3, developed vulvar irritation and pruritus one month before referring to our institution. She was referred to our center after appearing bilateral vulvar eczematoid lesions. Paget's disease was confirmed by biopsy. The Pap smear test, HPV testing, cervico-vaginal colposcopy, and abdominal-pelvic MRI before surgery were normal. Bilateral vulvectomy was done. Histologic evaluation revealed bilateral vulvar Paget's disease involving hair follicles. Surgical margins were involved by Paget's disease.

Case 3

A 52-year-old, gravida 3, para 3, postmenopausal woman was referred to our institution with vulvar itching and whitening in the past one year, received some medical

treatments (creams and ointments) without any response. Paget's disease was confirmed by biopsy. The Pap smear test, HPV testing, cervico-vaginal colposcopy, and abdominal-pelvic MRI before surgery were normal. Bilateral vulvectomy was done. Histologic evaluation revealed invasive vulvar Paget's disease in the background of massive in situ Paget's disease. Few foci of invasion in the superficial dermis were seen. The depth of dermal invasion was less than 1 mm. Paget's disease involved hair follicles ([Figure 3](#)). Surgical margins were involved by Paget's disease. Based on immunohistochemistry (IHC), human epidermal growth factor receptor 2 (HER-2), cytokeratin 7 (CK 7), and carcinoembryonic antigen (CEA) were positive. Melan A, human melanoma black 45 (HMB 45), transformation-related protein 63 (P63), fluido quístico mamario 15 (GCPDF-15), and S100 were negative.

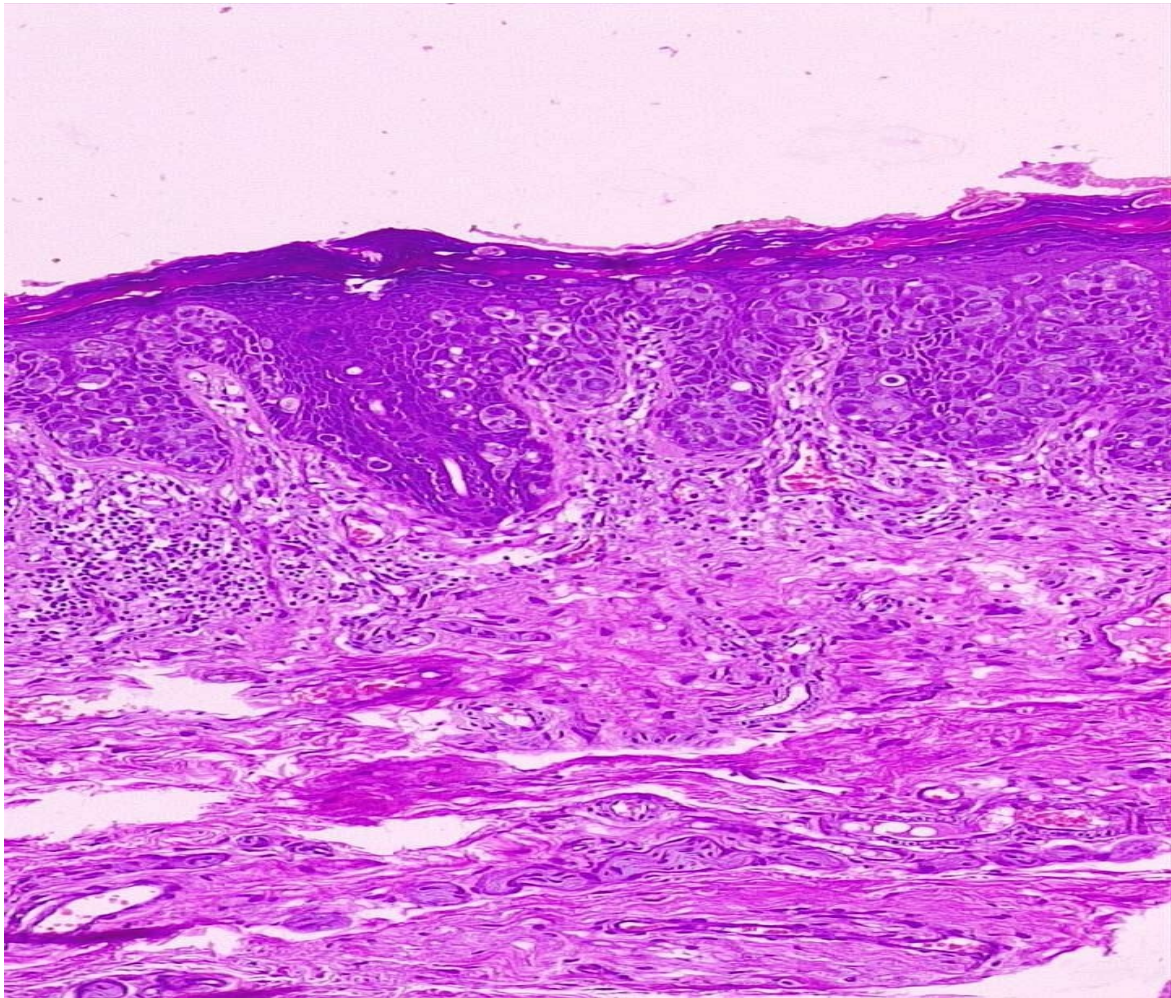


Figure 3. Paget's cells in the basal and above basal layer of the epidermis



Figure 4. Eczematoid lesion in the vulva bilaterally

Case 4

A 57-year-old, gravida 2, para 2, postmenopausal woman was referred to our center with a history of rheumatoid arthritis (treating with oral prednisolone) and a history of hysterectomy + left salpingo-oophorectomy (24 years ago) because of persistent vaginal bleeding. She reported vulvar itching and whitening and irritation from one month before ([Figure 4](#)). Paget's disease was confirmed by biopsy. Pap smear test, HPV testing, cervico-vaginal colposcopy, and abdominal-pelvic MRI before surgery were normal. Wide local excision was done. Histologic evaluation revealed

invasive vulvar Paget's disease involving hair follicles ([Figure 5](#)). Surgical margins were involved by Paget's disease. Based on IHC, epithelial membrane antigen (EMA) and Ki67 were positive, and HMB 45 and Melan A were negative.

She reported vulvar itching and a red ulcer (1 cm) one year after her surgery. Topical corticosteroid was described. Her lesion was improved after topical corticosteroid description.

Case 5

A 62-year-old postmenopausal woman, gravida 5, para 5, with a history of HTN, reported vulvar itching for the past one month. She had a red and white lesion in her left vulva based on our examination. Pap smear test, HPV testing, and cervico-vaginal colposcopy were normal. Paget's disease (involving hair follicles) was confirmed by excisional biopsy. Abdominal-pelvic imaging was normal. Left hemivulvectomy was done. Histologic evaluation revealed Paget's disease involving hair follicles ([Figure 6](#)). HMB45 and Melan-A were negative. Cytokeratin (CK) and CEA were positive. Lateral and deep surgical margins were free. Her surgery was performed seven years ago; she has been continuously under our follow-up so far, and she had no recurrence or problem in her follow-up period.

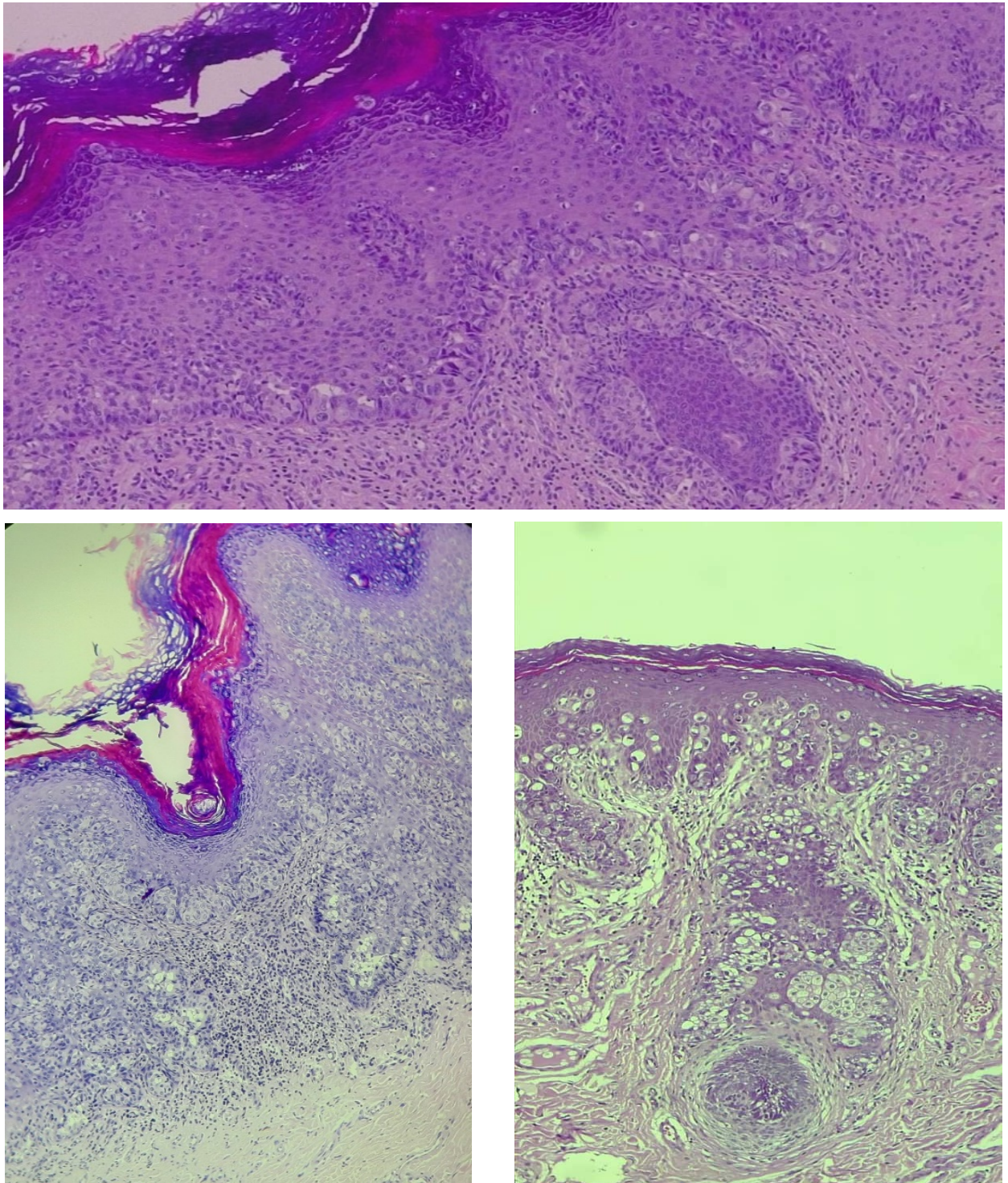


Figure 5. Extensive Paget's disease of the vulva

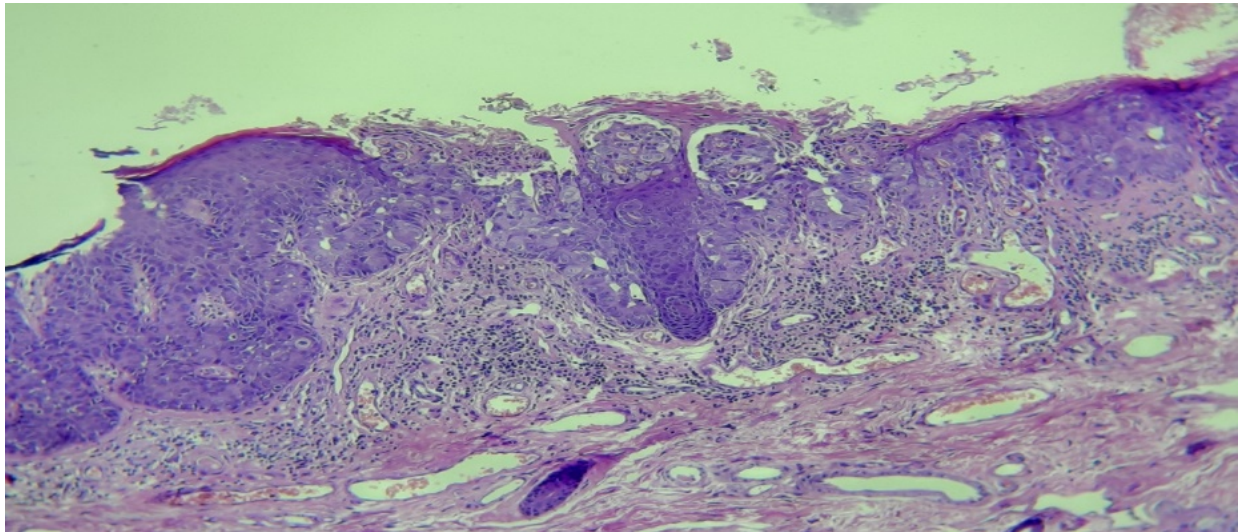


Figure 6. Paget's cells involved hair follicle

Discussion

In this study, five cases with Paget's disease were reported. The mean age of patients was 56.2 years, and all women were postmenopausal. Previous studies have reported that vulvar Paget's disease most commonly presents in postmenopausal women in their 50s (12, 13). In line with previous studies, the most common clinical symptoms in our cases were itching, whitening, irritation, and pruritus. In general, most patients receive various medical treatments (with creams and ointments) without any success. In previous studies, it has been reported that patients may also be asymptomatic or refer with chronic itching, bleeding, pain, soreness, and pruritus (13), as well as the presence of eczematous plate after various ineffective attempts of moisturizing and topical steroid creams with no favorable response (14).

In the current study, the interval between diagnosis and onset of symptoms was at least 7.8 months. In previously published studies, the diagnosis of the disease has been made almost 20 months after the onset of the disease that late diagnosis resulted in that the late diagnosis of the disease has resulted in larger lesions and higher recurrence rates. One of the causes of delayed diagnosis has been reported that common manifestations of Paget's disease with some benign diseases such as candidiasis, tinea cruris, contact dermatitis, psoriasis, lichen simplex and seborrheic dermatitis (1, 15).

All patients had normal Pap smear test, HPV testing, cervico-vaginal colposcopy, and abdominal-pelvic imaging before surgery. Some expressions of CK, CK 7, CEA, HER-2, EMA, and Ki 67 14 were observed in three patients examined in this study, while no expressions of HMB 45, Melan A, P63, GCPDF-15, and S100 were reported in patients. The differential diagnosis of primary and secondary Paget's disease

will be possible by IHC. Furthermore, to the many other disease entities that clinically resemble this malignancy, Paget's cells of vulvar origin express CK7 and carcinoembryonic antigen; however, those secondary to urothelial cancer are positive for CK20, p63, uroplakin III, and GATA-3, and those secondary to anorectal adenocarcinoma are positive for CK20, CDX2, and MUC2 but negative for CK7 (16).

In this study, patients with vulvar Paget's disease underwent surgery (bilateral vulvectomy, hemivulvectomy, and wide local excision). None of them postoperatively received adjuvant treatment with radiotherapy. The management of vulvar Paget's disease is often challenging (17). In Mujukian *et al.*'s study, surgery as vulvectomy and/or wide local excision with wide margins up to 1.5-2 cm) away from the visible lesion first line treatment (12). In a study by Loiacono *et al.*, all patients underwent surgery, including extended vulvectomy (42%), simple vulvectomy (33%), and wide local excision (25%). In the present study, surgical margins in 60% (3 of 5 cases) of the patients were involved by Paget's disease. In previously published studies, up to 70% of lesions had positive resection margins (18, 19).

In our study one patient two patients had IP and this finding is similar to that reported in other large series (19, 20). IP is a rare entity among patients with vulvar cancer, accounting for <1% of all vulvar malignancies (21). In the present study, patients were followed for at least seven years, and recurrence rate after surgery was 25% (1 of 5 cases). The median follow-up time in Loiacono *et al.*'s study was 39 months, ranging from 1 to 240 months (19), and recurrence rate was 32% after surgical excision (18).

In this study, five postmenopausal women with Paget's disease were reported. All patients had medical treatment before surgery without any benefit. The

mean time from onset of symptoms to diagnosis was shorter in this study compared with the previously published study. Perhaps one of the reasons for the low recurrence in this study was the early detection of Paget's disease. Our study showed that the primary treatment for vulvar Paget's disease remains surgery.

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Conflict of Interest

Authors declared no conflict of interests.

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