Recurrent Paget's disease of the vulva in a split-thickness graft

Romelyn April P. Imperio-Onglao, MD and Jericho Thaddeus P. Luna, MD, FPOGS, FSGOP
Department of Obstetrics and Gynecology, Philippine General Hospital, University of the Philippines-Manila

ABSTRACT

Extramammary Paget's disease (EMPD) of the vulva is a rare vulvar neoplasm but commonly arises during the postmenopausal period. Intraepithelial Paget's disease may persist for prolonged periods without demonstrating invasion but with high rates of recurrence. Appearance of Paget's disease in a split-thickness skin graft, is associated with an occurrence outside the grafted area. It demonstrates retrodissemination as the pathologic process hypothesized in the spread of the disease within the skin via lymphatics and vessels creating tissue bridges between sites of involvement. We present a case of an 81-year-old female, the patient came in for complaints of vulvar pruritus beginning at the left inguinal area three years prior to her diagnosis. She consulted with a dermatologist and was initially treated with steroids and emollients. Persistence of symptoms and enlargement of the lesion prompted a vulvar punch biopsy which showed Paget's disease and referral to the Gynecologic Oncology service. Wide local excision with split-thickness skin grafting was performed. However, one year after her surgery, patient noted vulvar pain and palpable vulvar lesions. Biopsy was done which showed Extramammary Paget's Disease recurrence. Patient underwent repeat wide local excision with frozen section, and split-thickness skin grafting. With the aid of frozen section, the intraepithelial involvement was noted to spread beyond the grossly apparent lesion. After 6 months post re-excision, patient noted vulvar pruritus and palpable vulvar lesions. Biopsy was done which showed Extramammary Paget's Disease recurrence. Due to the proximity of the lesion to the sphincter and need for a colostomy, the patient did not consent for re-excision. Imiquimod 5% was chosen as the mode of treatment. The challenges of interventions are to remove or treat disease that may not be visible, without overtreatment and to minimize morbidity from radical surgery. Surgery remains the primary management for EMPD of the vulva. Imiquimod 5% can be used in recurrences. Despite the advances in the knowledge and management of vulvar Paget's disease the high rate of recurrent disease remains a challenge for optimal management and would require frequent and long-term follow-up.

Keywords: Extramammary Paget's disease, vulva, vulvar neoplasm, Imiquimod 5%

INTRODUCTION

Paget's disease was eponymously named, after Sir James Paget, when he first described it in 1874 by as a rare intraepithelial neoplasm of the areolar skin. However, the pathognomonic, "cake-icing appearance" of vulvar Paget's disease was described in 1901 by Dubreuilj. The most commonly involved area in Extramammary Paget's Disease (EMPD) is the vulva, up to 65% of EMPD cases . Vulvar Paget's disease accounts for only 1% of vulvar malignancies, which leads to a limited understanding of the disease.[2]

Risk factors of EMPD of the vulva include caucasian race, genetic predisposition, previous radiation exposure, increased body mass index and history of hormone replacement therapy[3]. EMPD of the vulva is most commonly seen in postmenopausal women. In our tertiary institution, cases seen from 2008 were all menopausal, mostly between 50-80 years old, but with one patient at age 47 years old. All cases underwent surgical procedures such as wide local excision, with or without split-thickness skin-grafting.

Understanding the pathogenesis of EMPD remain equivocal. Embryologically, the cells of the stratum germinativum give rise to the skin appendages, including apocrine glands and the overlying squamous epithelium. Hence, the embryologic kinship is shown in the apocrine differentiation of the Paget cell (PC). However, cell origin remains controversial because EMPD, although mostly found on apocrine gland-bearing skin, can still be diagnosed on apocrine-poor sites.[4] Subsequently, a dermal factor that influences Pagetoid differentiation of the overlying dermis was theorized.

However, appearance of Paget's disease in a split-thickness skin graft have been reported and this runs counter the "pagetoid factor" in the underlying dermis. A theory that might explain this behavior accounts for "retrodissemination" and may take place within the skin

via lymphatics or other vessels creating normal tissue bridges between sites of involvement. This is also called the "spray pattern" hypothesis and underscores the unusual spread pattern of this disease entity[5]. Moreover, Gunn and Gallager[6] postulated that the growth characteristics of PCs exhibit polycentric growth, irregular growth morphology, and histological boundaries often exceed the boundaries of clinical signs. Paget cells may be present along the basement membrane far beyond the apparent border of the lesion or even multicentric in location, which could account for the local recurrences typical of patients already treated by wide local excision.

Clinically, EMPD of the vulva presents as an erythematous lesion, often involving the vestibule and adjacent areas. EMPD of the vulva can also present as an eczematous lesion, reddish to pink with white islands of hyperkeratosis and usually involving hair-bearing skin[7]. The extent of involvement can be varied from very focal, or extensive until the anus, medial aspects of the upper thigh, or other contiguous sites. EMPD often presents as a solitary lesion but can manifest as multiple plaques separated by areas of normal skin. Pruritus is present in more than half the patients and was present for a median duration of 2 years before the diagnosis.[8] Differentials include superficial fungal infections, psoriasis, and various eczematous dermatoses. Due to the nonspecific presentation, EMPD of the vulva is often initially treated with various topical medications for some time before the diagnosis is made by biopsy, which contributes to the delay in definitive management.

Histopathologic examination of vulvar EMPD with hematoxylin and eosin stain show an intraepithelial proliferation of large round cells with abundant, pale-staining, basophilic cytoplasm and large, centrally situated nuclei, and occasionally a prominent nucleolus. The cells are often concentrated in the lower epidermis but may scatter higher. The paget cells can be distributed singly or clusters, nests, or glandular structures within the epidermis and epithelium of adnexal structures. Hyperkeratosis, acanthosis, and parakeratosis may be observed as well. Inflammatory small round cells and plasma cells can also be found in the upper dermis.

Wilkinson and Brown subclassified Paget's disease of the vulva into primary or secondary disease[9]. Primary Paget's disease is of vulvar cutaneous origin. Secondary vulvar EMPD is arises from a non-cutaneous internal neoplasm, either by direct extension or by epidermotropic metastases from an underlying malignancy of the gastrointestinal tract, of the urogenital tract, or of an adenocarcinoma originating elsewhere.

Paget's disease of the vulva is often limited to the epidermis and mucosa without invasion. There have been a few documented cases of progressive dermal invasion from initial purely intraepithelial vulvar disease over an extended follow-up period of greater than 10 years, with subsequent lymphatic metastases; thus showing that primary disease has the potential to become disseminated. Hence, EMPD of the vulva is further classified into 3 subtypes: Type 1a, intraepithelial Paget disease; Type 1b, intraepithelial Paget disease with invasion; and Type 1c, intraepithelial Paget disease with an underlying adenocarcinoma of a skin appendage or a subcutaneous gland. In invasion, histopathologically, dyscohesive neoplastic Paget cells are seen infiltrating the underlying dermis or submucosa. Although the degree of malignancy of EMPD is low, the deeper the infiltration of Paget cells, the lower the survival rate of patients.[10]

Paget cells express Cytokeratin 7 (CK7), Cytokeratin, carcinoembryonic antigen, gross cystic disease fluid protein 15, human epidermal growth factor receptor 2, carbohydrate antigen 125, and androgen receptors, but do not express markers of squamous cell differentiation, such as p63 and p40, and melanocyte markers, such as Melan-A, Human Melanoma Black- 45, or S100 proteins. P53 protein overexpression in the intra- epidermal component is associated with invasion. Uroplakin-III, CK7 and CK20 and GATA3 gene are expressed in Paget disease secondary to urothelial carcinoma. CK20, Homeobox protein CDX-2, and Mucin 2 positivity (but not CK7) might indicate an underlying anorectal adenocarcinoma.[11]

EMPD of the vulva can occur with a synchronous or metachronous neoplasm: colorectal adenocarcinoma, cervical adenocarcinoma, carcinoma of the transitional epithelium from the renal pelvis to urethra, breast and vulvar carcinoma. Routine screening with colonoscopy, Pap test, mammogram and cystoscopy is therefore recommended. There have been reports of an association with distant tumors, particularly breast cancer, although the strength of this association is unknown.

The optimal management of Paget's disease of the vulva remains unclear. Surgical excision is usually the primary therapy. Primary cutaneous Paget disease is usually treated with total excision of the visible lesion, with a 1- to 3-cm margin of excision and excision to the fascia to exclude invasion or underlying skin appendage adenocarcinoma[12], or vulvectomy with wide margins up to 1.5-2cm away from visible lesion[13]. The lesions often extend past clinically apparent borders resulting in positive margins up to 50-70%.[14] Surgical excision is also limited by the anatomy of the vulva. However, seemingly adequate local resections showed no association between positive margins following primary surgery and recurrence.

Paget's disease of the vulva develop multiple recurrences regardless of treatment modality or margin status[15,16]. Recurrence rates appear high despite conventional surgical treatment, from 8% to 33% likely

due to the multifocal nature of the disease and ill-defined margins[17]. Interestingly, recurrences up to 12 years after initial treatment have been reported.

Extramammary Paget's disease of the vulva may recur in an area previously totally excised and transplanted with autologous skin, as documented in six cases[18-22]. The recurrence in these cases varied from as early as 1 year after surgery, to 9-11 years after surgery. The precise histogenesis of the disease is not completely understood.

CASE

The case is an 81-year-old Filipina patient, Gravida 5 Para 5, previously diagnosed with Breast carcinoma stage IIA, who underwent modified radical mastectomy. She has been breast cancer free for four years. Primarily, the patient came in for complaints of vulvar pruritus beginning at the left inguinal area three years prior to her diagnosis. She consulted at the Division of Dermatology and was treated as a case of fungal infection and lichen simplex chronicus. Patient was treated with steroids and emollients. Patient was lost to follow up due to temporary resolution of symptoms. On subsequent consult for recurrent pruritus, the dermatologist noted the lesion to have the "icing on the cake" pathognomonic sign, with an underlying erythematous plaque measuring 8.0 x 12.0 cm involving the left labia majora up to the gluteal area inferiorly. There was a 1.5 cm margin from the left genitocrural fold laterally, crossing the midline to the clitoris and right labia majora. Physical examination showed no distal urethral involvement, smooth vagina, cervix measured 1.0 x 1.0 cm and smooth; corpus small, no adnexal masses or tenderness, bilateral parametria smooth and pliable. Vulvar punch biopsy was done which showed Paget's disease. Patient was referred to the Division of Gynecologic Oncology and was advised surgery. Metastatic work up was done to prepare the patient for surgery.

For patients with vulvar EMPD, a reasonable initial work-up includes screening for genitourinary and gastrointestinal tract involvement as well as breast disease. The patient underwent a complete pelvic examination (including Pap smear and colposcopy), colonoscopy, cystoscopy (done intraoperatively), abdominopelvic ultrasound, transvaginal ultrasound, chest x-ray and mammography. All results were unremarkable.

Patient underwent wide local excision. Intraoperatively, there were no palpable bilateral inguinal lymphadenopathies. The lesion appeared as an erythematous plaque which measured 8.0 x 12.0 cm, and spanned from the left labia majora, extending to the gluteal area inferiorly, crossing the left genitocrural fold laterally by 1.5 cm, and across to the right labia majora. There was no distal urethral involvement. A 1 cm margin was marked around the lesion using India ink. Intraoperative cystoscopy was done by the Division of Urology. Aiming for negative margins, a depth of 1-cm was excised towards the subcutaneous tissue, superiorly towards the mons pubis, 3 cm distal to the left genitocrural fold, between the right labia and right genitocrural fold, and inferiorly until the perineal body. The excised specimen measured 27.5 x 12.5 x 1 cm. Plastic surgery performed split-thickness grafting. Harvest of the split-thickness skin graft was taken from the right leg. Suturing of the flap of the donor skin to the recipient bed was done using a skin stapler. Hydrocolloid and epinephrine were applied to the donor site. Bolster dressing was done.

On histopathologic assessment of the specimen, it was signed out as Extramammary Paget's disease of the vulva, 13 centimeters in greatest tumor dimension. The following areas were positive for Paget's tumor: clitoris, anterior skin margin, anterior fourchette margin, left labial margin and right labial margin. The plan then was to observe, and to perform resection once recurrence occurs. Patient had good follow up for the first three months. However, due to financial constraints, patient was lost to follow up.

One year after her surgery, patient noted vulvar pain and palpable vulvar lesions, (1) 1.0 x 1.0 cm lesion at the right side of the introitus, and a (2) 3.0 x 1.0 cm lesion at the left side of the posterior fourchette. On consult, there was note of a hypertrophic scar along the genitocrural fold and the lower border of the mons pubis. There was a 1.0 x 1.0 cm beefy-red mass at the 11 o'clock position of the vaginal introitus, about 1 cm from the urethra, and a 2.0 x 1.0 cm beefy-red mass at the 5-6 o'clock position of the vaginal introitus. On internal examination, the cervix measured 2.0 x 2.0 cm, smooth, corpus small, there were no adnexal masses, and the bilateral parametria smooth and pliable. Biopsy was done on both sites, which showed Extramammary Paget's Disease recurrence. Metastatic work up was done to prepare the patient for surgery.

Patient underwent repeat wide local excision with frozen section. Intraoperatively, there were no palpable bilateral inguinal lymphadenopathies. There was no distal urethral involvement. A 1-cm margin was marked around the lesions at the 11 o'clock and 6 o'clock positions using India ink. However, intraoperatively, there was note of an erythematous plaque with "cake-icing" between the two lesions, extending from the right side of the vaginal introitus towards the perianal area. The patient had a negative colonoscopy prior to the procedure. Apart from intraoperative cystoscopy done by the Division of Urology, the Division of Colorectal surgery also assessed the patient for possible involvement of the sphincter. The first excised mass from the 11 o'clock lesion revealed a positive inferior

margin, as well as the second excised mass from the 6 o'clock tumor revealed positive margins from the areas near the vaginal introitus and gluteal area. Further sections were taken until the frozen section revealed negative margins. The final excised area extended from the area proximal to the introitus until the right gluteal region, with sparing of the sphincter. Majority of the recurrence occurred in the area of the previous split-thickness skin graft. Plastic surgery performed primary closure of the defect in the left gluteal area and split thickness grafting across the defect in the right gluteal region. Harvest of the split-thickness skin graft was taken from the left leg. Suturing of the flap of the donor skin to the recipient bed was done using a skin stapler. Hydrocolloid and epinephrine were applied to donor site. Bolster dressing was done. Patient had good wound healing.

Patient had regular monthly follow up. Six months post re-excision, the patient noted pruritus on the left gluteal area. On examination, a hypertrophic scar from the lower border of the mons pubis, along the bilateral genitocrural folds could be observed. The vaginal introitus is partially everted but smooth and covered with atrophic epithelium. Proximal to the anal sphincter, at the left gluteal area is a 5 x 3 cm beefy-red mass with the pathognomonic icing-on-the-cake appearance at 4-6 o'clock position. On internal examination, the cervix measured 2.0 x 2.0 cm, smooth, corpus small, there were no adnexal masses, and the bilateral parametria smooth and pliable. Biopsy was done on the mass, and once again it showed Extramammary Paget's Disease recurrence. It is important to note that biopsy of the normal appearing skin surrounding the lesion's periphery was done, and these were positive for Extramammary Paget's Disease recurrence as well.

Patient was initially amenable to re-excision due to the pruritic symptoms. However, on metastatic work up and assessment by Colorectal Surgery, a colostomy was suggested due to the lesion's proximity to the sphincter. The patient did not consent to a colostomy. She is being managed medically with Imiquimod 5%.

DISCUSSION

The patient is a postmenopausal woman with a history of breast cancer, currently in remission. There have been reports of an association with distant tumors, particularly breast cancer, although the strength of this association is unknown. Patients with EMPD of the vulva are at inherent risk for a second synchronous or metachronous neoplasms which warrant work-up[23]. CT imaging, colonoscopy, cystoscopy and pap smear have showed no involvement of the rectum or bladder for this patient. A mammogram was also done to document remission from breast cancer.

Patient had no evidence of breast cancer when Paget's disease of the vulva was diagnosed. Several small studies in literature aim to characterize a series of mammary-like diseases by using an immunohistochemical algorithm that identifies the major molecular subtypes of breast cancer. IHCs such as estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), Ki67, epidermal growth factor receptor (EGFR), cytokeratin (CK) 5, nestin, and inositol polyphosphate-4-phosphatase (INPP4b) were used. These suggest that breast cancer subtyping can be applied to vulvar mammary like diseases such as Paget's. Nevertheless, these IHCs could be explored in future cases which may also present with association of breast cancer.

The patient initially presented with pruritus and pain. Due to the clinical resemblance to a dermatosis, the patient was treated with various topical medications for some time before the diagnosis is made by biopsy. These signs and symptoms are consistent with the cases in literature, which experience delay in diagnosis and management[24]. Eventually the pathognomonic "icing on the cake" sign became evident in the patient, with an underlying erythematous plaque measuring 8.0 x 12.0 cm involving the left labia majora up to the gluteal area inferiorly (Figures 5 and 6). The extent of involvement started as focal, but due to the delay in management, became very extensive. There was a 1.5 cm margin from the left genitocrural fold laterally, crossing the midline to the clitoris and right labia majora.

Histopathologic examination of the vulvar biopsy from this patient with hematoxylin and eosin stain revealed glandular spaces and intraepithelial proliferation of large round cells with abundant, pale-staining, basophilic cytoplasm and large, centrally situated nuclei, sometimes with a prominent nucleolus. The cells were found below the epidermis. In Figure 1, double headed arrows delineate the full thickness of the epidermis. The encircled structures show the presence of glandular spaces in the epidermis. Normally, only stratified squamous keratinizing cells occupy this area. The boxed areas show areas of hypercellularity which at this magnification are probably inflammatory cells.

On LPO in Figure 2, most of the cells seen are Paget cells. The area enclosed by the box are the only residual squamous cells of the epidermis. Everything else surrounding it are Paget cells. These can occur as single cells or in clusters. Arrows point at mitotic figures. The Paget's disease is an in-situ/intraepithelial neoplasm, as the interface of the epidermis and dermis can be appreciated and the tumor has not breached the basement membrane which can be seen intact as pointed by the arrow heads.

Figure 3 shows a higher power magnification which allows assessment of the cytologic features of the tumor

cells. These have moderate to abundant eosinophilic cytoplasm with indistinct cell borders (Squamous cells shows show well-defined borders and intercellular bridges). Arrowheads point at nuclei, arrows point at nucleoli. The pink substance surrounding the nuclei is the cytoplasm. Nuclei vary in size and shape (atypical and pleomorphic) with vesicular/open nuclei, connoting active transcription by the tumor cells, and prominent nucleoli. The surrounding smaller blued dots are nuclei of lymphocytes.

Immunohistochemistry guides the diagnosis for Paget disease. Immunohistochemical staining for CK20 was performed. For this case, CK20 was negative as shown in Figure 4. If secondary Paget of the vulva from a colorectal primary, the tumor cell nests should stain brown.

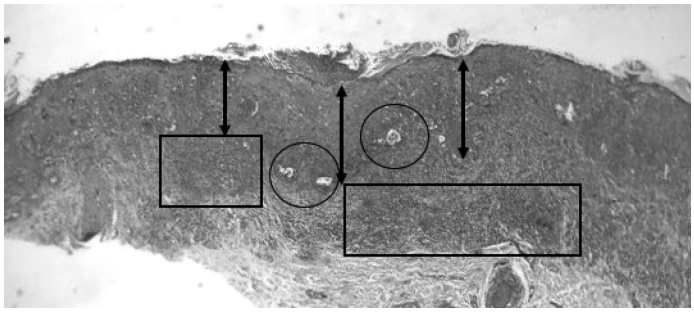

Figure 1. Scanning magnification of the skin showing Paget's disease. The double headed arrows delineate the full thickness of the epidermis. The encircled structures show the presence of glandular spaces in the epidermis. Normally, only stratified squamous keratinizing cells occupy this area. The boxed areas show areas of hypercellularity which at this magnification are probably inflammatory cells.

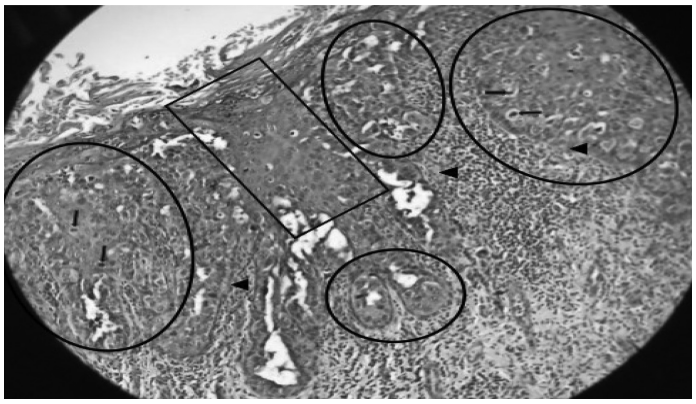

Figure 2. LPO magnification of the skin showing Paget's disease. Most of the cells seen are Paget cells (PC). The area enclosed by the box are the only residual squamous cells of the epidermis. Everything else surrounding it are Paget cells. These can occur as single cells or in clusters. Arrows point at mitotic figures. Paget's disease is an in-situ/intraepithelial neoplasm. What this means histologically, one can still define the interface of the epidermis and dermis because the tumor has not breached the basement membrane which can be seen intact as pointed by the arrow heads.

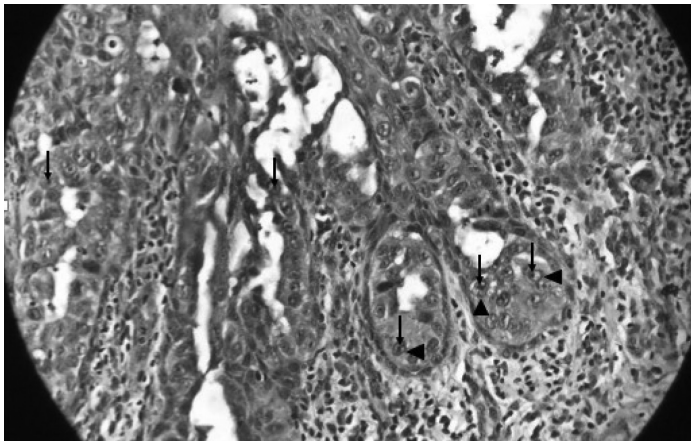

Figure 3. HPO magnification of the skin showing Paget's disease. These have moderate to abundant eosinophilic cytoplasm with indistinct cell borders (Squamous cells shows show well-defined borders and intercellular bridges). Arrowheads point at nuclei, arrows point at nucleoli. The pink substance surrounding the nuclei is the cytoplasm. Nuclei vary in size and shape (atypical and pleomorphic) with vesicular/open nuclei, connoting active transcription by the tumor cells, and prominent nucleoli. The surrounding smaller blued dots are nuclei of lymphocytes.

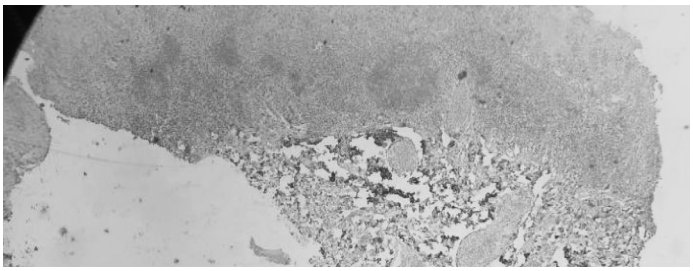

Figure 4. IHC staining for CK20

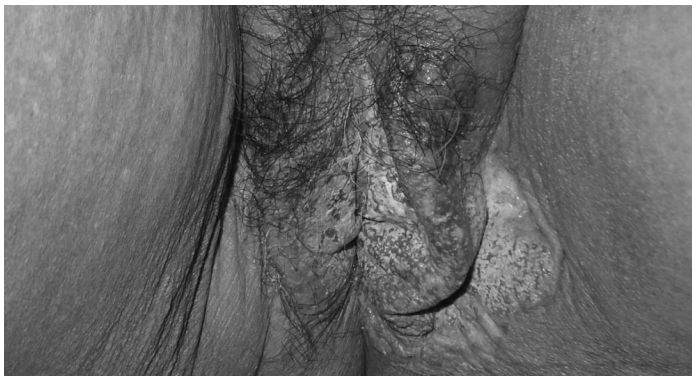

Figure 5. Paget's disease

Figure 6. Cake-icing effect

Surgical excision has long been recommended as the standard treatment strategy for primary or recurrent EMPD. Historically, these procedures have ranged from the extensive and aggressive radical vulvectomy with skin grafting for reconstruction, to the more conservative (and common) wide local excision.[25] Regardless of approach, the data demonstrate high recurrence rates ranging from 30 to 60%, likely due to the presence of subclinical multifocal microscopic diseas. The initial wide local excision produced an excised specimen measured 27.5 x 12.5 x 1 cm (Figure 7) which on histology had a widest tumor diameter of 13 cm. No frozen section was utilized during the initial excision, which echoed the inferences from cases in literature that margin status did not confer a better prognosis with regards to recurrence. Final histopathologic reading showed the following areas were positive for Paget's tumor: clitoris, anterior skin margin, anterior fourchette margin, left labial margin and right labial margin. The anatomy of the vulva confers limitations in terms of maximum tissue to be excised around these areas. Increasing removal of additional tissue confers an increased risk of wound dehiscence. The plan then was to observe, and to perform resection once recurrence occurs.

After one year, the disease recurred, and a multifocal configuration was more apparent involving the split-thickness skin graft. The patient presented with a 1.0 x 1.0 cm lesion at the right side of the introitus, and a (2) 3.0 x 1.0 cm lesion at the left side of the posterior fourchette. The hypertrophic scar along the genitocrural fold and the lower border of the mons pubis were observed. There was a 1.0 x 1.0 cm beefy-red mass at 11 o'clock position of the vaginal introitus, about 1 cm from the urethra, and a 2.0 x 1.0 cm beefy-red mass at the 5-6 o'clock position of the vaginal introitus (Figure 9). The recurrent lesions in this patient were multiple plaques which seemed to be separated by areas of normal skin but on frozen section/ histopathologic assessment showed underlying Paget cells.

Wide local excision often leaves large defects and can pose as challenges for primary closure (Figure 10). The split-thickness skin graft by the Division of Plastic Surgery survived completely with no complication from the first surgery and the re-excision. (Figures 8 and 11). There was good graft reception in the patient, and there was only temporary postoperative discomfort upon sitting and stretching of legs (Figure 12).

Recurrence in a split-thickness skin graft is a rare occurrence. The possibility of retro-dissemination occurred, and that Paget cells migrated from the disease-preserved skin into the graft site is more likely. The propensity for recurrent disease for this case may also be explained by the multicentric origin of this lesion. This theory could further be underscored since there were areas of normal tissue in between the multifocal recurrences. Spread via lymphatics or other vessels, creating a "spray pattern" demonstrated the unusual spread pattern of this disease entity. Another theory could be, as previously mentioned, was the association with distant tumors, particularly breast cancer, or the concept of "mammary-like diseases."

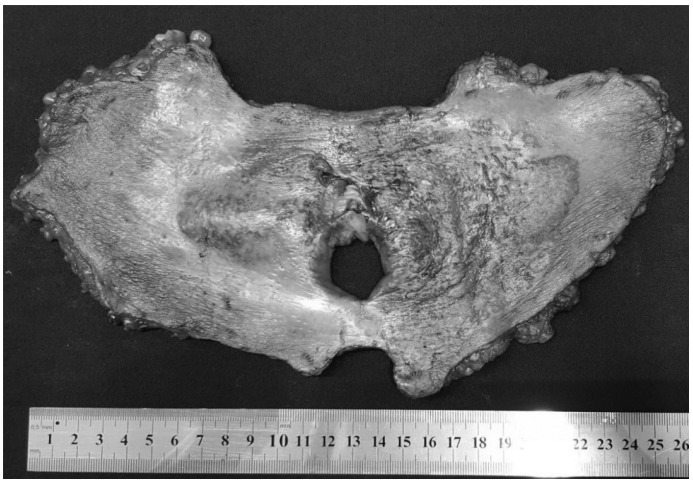

Figure 7. Primary excision of Paget's Disease

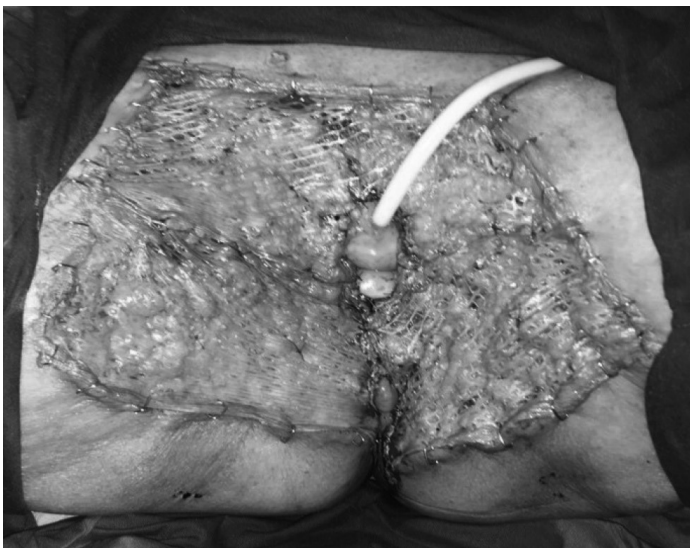
Figure 8. Split-thickness skin graft during first excision

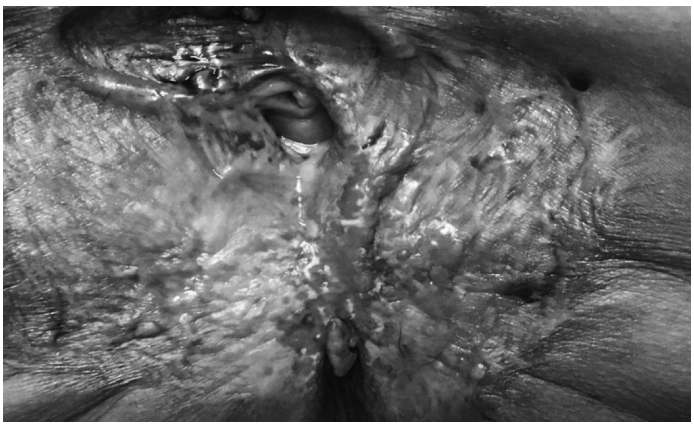
Figure 9. Paget's Disease Recurrence in a split-thickness skin graft

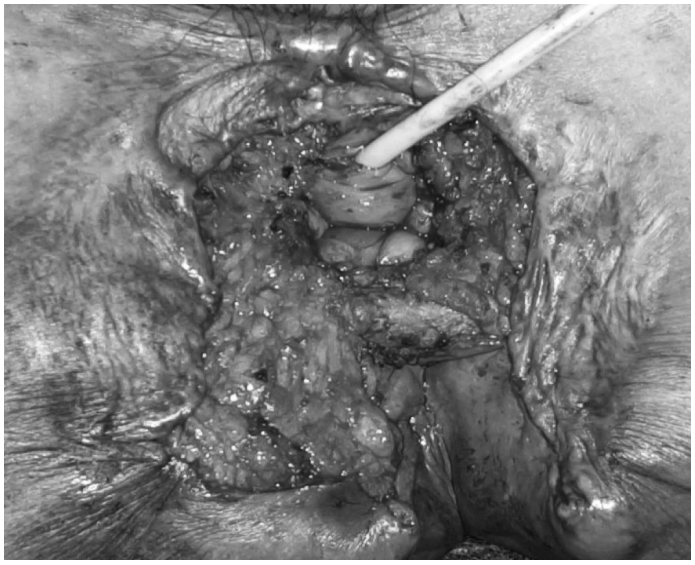

Figure 10. Post re-excision, prior to skin grafting

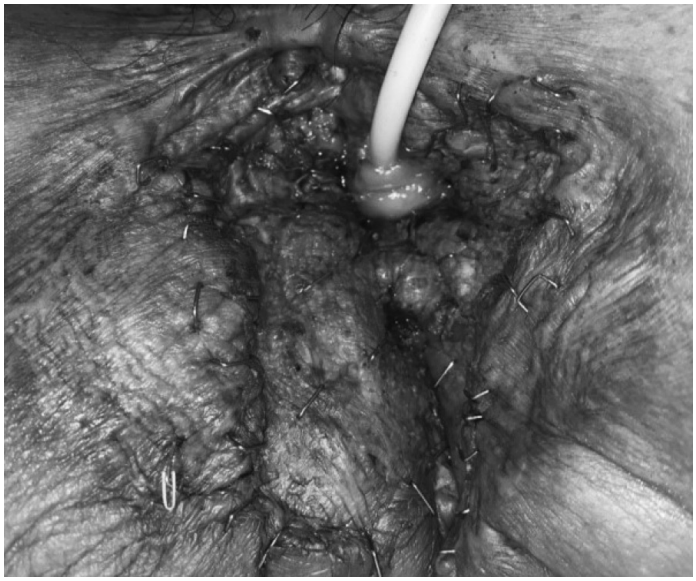

Figure 11. Post excision with skin graft post-op Day 2

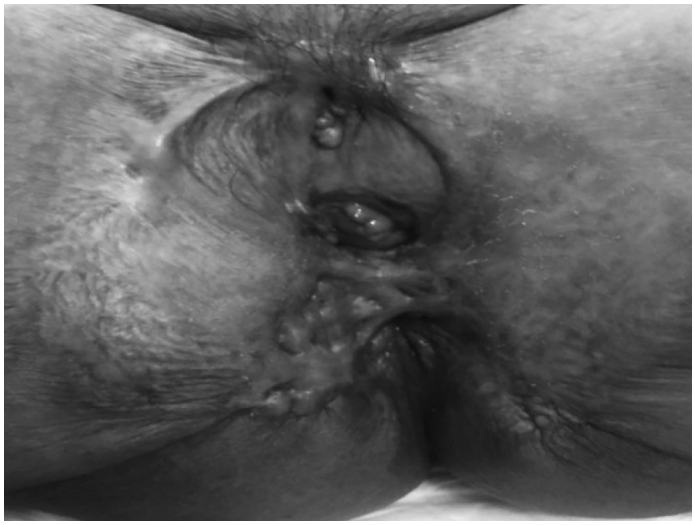

Figure 12. Follow up post three months after re-excision (post recurrence)

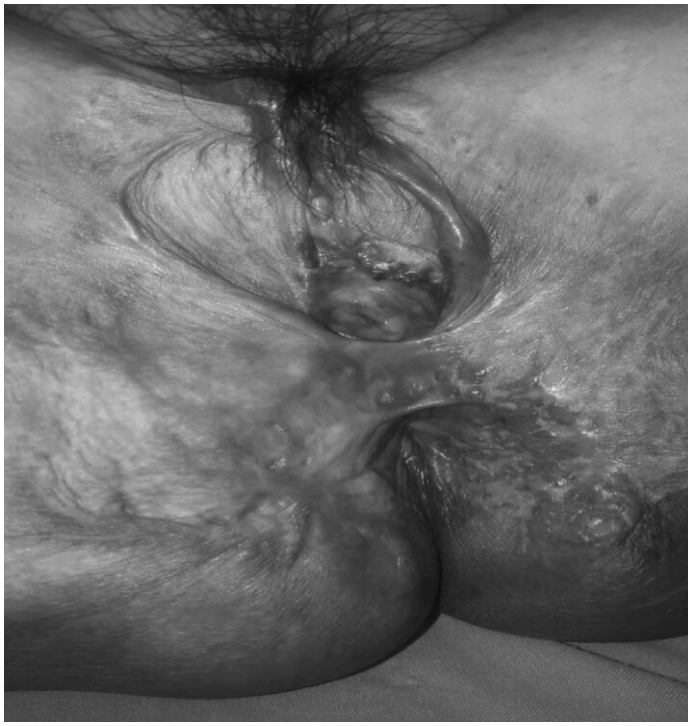

Figure 13. Recurrence in the Skin graft. Follow up 6 months after re-excision

Medical or other treatment modalities have been used for EMPD due to the high recurrence rates despite adequate surgery. Topical therapies including 5-fluorouracil (5-FU), bleomycin, and imiquimod have been used to treat EMPD. Unfortunately, 5-FU and bleomycin are associated with poor response rates and toxic side effects. Imiquimod is an anti-tumor immune response-modifying agent that activates toll-like receptor 7 (TLR7) and results in cytokine release and activated CD8 (+) T cells. Imiquimod appears to modify the biologic response to the tumor cells, enhancing immune function. The mechanism of imiquimod in treating these conditions is not fully understood. While imiquimod has no direct antiviral activity in cell culture, mouse skin studies suggest that imiquimod induces cytokines, such as interferon-α. In a study by Cowan, a complete clinical and histologic remission was observed in 6 (75%) women at the 12-week follow-up visit after using imiquimod cream for recurrent Paget's of the vulva.[26] In the study of Sawada in 2017, imiquimod was applied three times per week for 16 weeks. The response rate of imiquimod 5% cream for nine patients with EMPD was 100%, with five (56%) achieving complete remission[27]. Topical imiquimod 5% cream was first reported as a treatment for primary and recurrent EMPD of the vulva in 2002 and 2003, respectively, and has since been documented in over 60 reports. Machida and colleagues recently conducted a systematic review on the effects of imiquimod on primary and recurrent vulvar EMPD. They recommended that imiquimod be considered

for patients with recurrent disease who have undergone multiple surgical resections or are poor candidates for surgery. Hence, imiquimod 5% cream can also be used for tertiary and quaternary recurrences.

Other methods: 1) Photodynamic therapy works by the exposure of sensitized cells to a specific wavelength of light, which activates a cascade of photochemical and photobiological events, causing irreversible damage to tumor tissue. Photodynamic therapy is prone to cause local pain and inflammation in patients[28], so it has not been widely promoted, but there are still few case reports abroad that have obtained good results after photodynamic therapy with improved technology. 2) Radiotherapy destroys tissues by damaging deoxyribonucleic acid (DNA), affecting normal as well as abnormal tissues. The results of radiotherapy as adjuvant therapy has shown poor prognosis. In the study by Chenyu, they concluded that radiotherapy is not effective for patients with EMPD of the vulva because there is no standard dose and course of treatment. 3) Carbon dioxide (CO2) laser has been used initially for treatment of disease of the cervix. The depth of destruction can be controlled and planned but needs to be deep enough to decrease the likelihood of recurrence. Non-surgical treatments are often used as an alternative treatment for patients with large lesions, or cannot be operated on. The disadvantages are that the corresponding pathological results cannot be obtained, and the patient's condition and prognosis cannot be evaluated, so often it is not preferred as the primary treatment options.

Unfortunately, there are no published guidelines regarding need and frequency of follow-up in cases of primary EMPD. In addition, no consensus exists pertaining to subsequent internal malignancy screening if the initial one is negative.[29] A reasonable approach to an initially diagnosed primary noninvasive EMPD would be a clinical evaluation twice a year for the first 3 years then once yearly thereafter. The follow up schedule employed for this patient, in conjunction with the local guidelines was every 3 months until the most recent recurrence. The patient will follow up every month to note the response of the lesion to Imiquimod.

CONCLUSION

In this case, re-excision with the aid of frozen section, the involved tumor has spread from the grossly apparent lesion across the skin-graft demonstrated the pathologic process hypothesized in retrodissemination within the skin via lymphatics or other vessels creating normal tissue bridges between sites of involvement.

Primary treatment for Paget's disease of the vulva remains surgical though alternative therapies exist, and the optimal management currently remains unclear.

The present case represents the earliest reported case of extramammary Paget's disease recurrence, only after 6 months of re-excision, and only the seventh overall documented in literature occurring in a skin-graft. Another study showed of recurrence in 3 months post skin-grafting, but the recurrence occurred in the base of the bladder[30].

The finding that such a situation can arise mandates careful follow-up in patients with EMPD of the vulva. Apart from the early incidence of recurrence, our study has no other novelties compared to other studies, but could serve to emphasize once again the delay with which this pathology is often diagnosed and the need to establish further therapeutic alternatives, considering the large number of relapses with repeated surgical treatments and consequent impact on the quality of life of the patient. ■

REFERENCES

1. Cherry O. Onaiwu Mila Pontremoli Salcedo Suzana A. Pessini Mark F. Munsell Elizabeth E. Euscher e, a. K. (2017). Paget's disease of the vulva: A review of 89 case s. *Gynecologic Oncology Reports*, 46-49.

2. Destin Black a, C. T. (2007). The outcomes of patients with positive margins after excision for intraepithelial Paget's disease of the vulva Destin Black a, Carmen Tornos b, Robert A. Soslow b, Christopher S. Awtrey. *Gynecologic Oncology*, 547-550.

3. Robert J. Kurman, L. H. (2011). *Balustein's Pathology of the Female Genital Tract.* New York: Springer.

4. James Fanning, D. H. (1999). Paget's disease of the vulva: Prevalence of associated vulvar adenocarcinoma, invasive Paget's disease, and recurrence after surgical excision. *American Journal of Obstetrics and Gynecology*, 24-27.

5. Renee A. Cowan a, D. R.-R. (2016). A pilot study of topical imiquimod therapy for the treatment of recurrent extramammary Paget's disease. *Gynecologic Oncology*, 1-5.

6. Katharine A Edey, E. A. (2014). Interventions for the treatment of Paget's disease of the vulva. *The Cochrane Collaboration*. 2014; 1-25.

7. Cherry O. Onaiwu, Mila Pontremoli Salcedo, Suzana A. Pessini, Mark F. Munsell, Elizabeth E. Euscher e, a. K. (2017). Paget's disease of the vulva: A review of 89 cases. *Gynecologic Oncology Reports*, 46-49.

8. Christina Lam, M. D. (2010). Extramammary Paget's Disease: Summary of Current Knowledge. *Dermatologic Clinics*, 807-826.

9. Shepherd V, D. E.-H. (2005). Extramammary Paget's disease. *BJOG*, 273-279.

10. J. K. (2007). Mammary and extramammary Paget's disease. *Journal of the European Academy of Dermatology and Venereology*, 581-590.

11. Zollo JD, Z. N. (2000). The Roswell Park Cancer Institute experience with extramammary Paget's disease. *British Journal of Dermatology,* 59-65.

12. Edey KA, A. E. (2019). Interventions for the treatment of Paget's disease of the vulva (Review). Cochrane Library, Issue 6. Art. No.: CD009245.

13. Edward J. Wilkinson, M. H. (2002). Vulvar Paget Disease of Urothelial Origin: A Report of Three Cases and a Proposed Classification of Vulvar Paget Disease. *Elsevier Science*, 549-554.

14. Geisler J. P. (1995). Extramammary Paget's Disease of the Vulva Recurring in a Skin Graft. *Gynecologic Oncology Elsevier*, 446-7.

15. Beecham C. (1976). Paget's Disease of the Vulva: Recurrence in Skin Grafts. *Obstetric and Gynecology*, 55-58.

16. Misas J. (1990). Recurrent Paget disease of the vulva in a split-thickness graft. *Obstetrics Gynecology*, 543-544.

17. Jonge E. D. (1988). Recurrent Paget's Disease of the vulva after simple vulvectomy and skin grafting. *South African Medical Journal*, 46-47.

18. N. Hatta, *. M. (2007). Extramammary Paget's disease: treatment, prognostic factors and outcome in 76 patients. *British Association of Dermatologists*.

19. Rosalia Maria Rita Loiacono M. (2019). Paget disease of the vulva an analysis of 24 cases. *Medicine Wolters Kluwer,* 1-4.

20. Ian S.C. Jones a, b. (2011). Paget's disease of the vulva: Diagnosis and follow-up key to management; A retrospective study of 50 cases from Queensland. *Gynecologic Oncology Elsevier*, 42-44.

21. Cherry O. Onaiwu a, P. T. (2014). Invasive extramammary Paget's disease of the bladder diagnosed 18 years after noninvasive extramammary Paget's disease of the vulva. *Gynecologic Oncology Case Reports Elsevier*, 27-29.

22. Angela Mujukian A. I. (2019). xtensive extramammary Paget's disease of the vulva involving the bladder postradical split skin graft reconstruction. *BMJ Case Report*, 12.

23. Gunn RA, G. H. (1980). Vulvar Paget's disease: a topographic study. *American Cancer Society*, 590-4.

24. Chenyu Z. (2018). Clinical analysis of 36 cases of primary vulvar Paget disease. *Chinese Journal of Obstetrics and Gynecology,* 540-546.

25. Karam A, D. O. (2012). Treatment outcomes in a large cohort of patients with invasive Extramammary Paget's disease. *Gynecologic Oncology*, 346-51.

26. Masahide SAWADA J. K. (2017). Imiquimod 5% cream as a therapeutic option for extramammary Paget's disease. *The Journal of Dermatology*, 1-4.

27. DiSaia P. J. (1995). A Report of Two Cases of Recurrent paget's Disease of the Vulva in a split-thickness graft and its possibl pathogenesis-labeled retrodissemination. *Gynecologic Oncology*, 109-112.

28. Michelle van der Linden M. M. (2018). Vulvar Paget disease: A national retrospective cohort study. *American Academy of Dermatology*, 1-7.

29. Dimitrios Nasioudis M. B. (2019). Extramammary Paget disease of the vulva: Management and prognosis. *Gynecologic Oncology*, 1-5.