Extensive extramammary Paget's disease of the vulva involving the bladder postradical split skin graft reconstruction

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DESCRIPTION

An 84-year-old woman presented to the gynaecology department with a 9-month history of vulval soreness, irritation and bleeding. Her medical history included Dukes C sigmoid adenocarcinoma, thyroid malignancy and multiple medical comorbidities including atrial fibrillation and ischaemic heart disease. The patient was a heavy smoker. On pelvic examination, there was a large erythematous plaque affecting the right labia majora, and biopsies (figure 1) confirmed vulval extramammary Paget's disease (EMPD). Topical Imiquimod (TLR-7 inhibitor) was initially started with minimal response. The patient then underwent a wide local excision and had several local recurrences excised over the next few years. Finally, the patient required radical excision with a split skin graft reconstruction 6 years after original diagnosis. Three months following the radical procedure, the patient complained of vulval pain, haematuria and urethral spasm. Cystoscopy of the bladder revealed a trabeculated mucosa with a 1 cm raised pale lesion. The lesion was biopsied and confirmed to show recurrent vulval EMPD with disease extension involving Paget's cells in the urethra (figure 2) and base of the bladder. Following urology review, a decision was made that in view of the patient's performance status and in keeping with her wishes she was not eligible for advanced treatment options such as radiotherapy. She was therefore referred to palliative and pain services for best supportive care.

Figure 1 Vulval Paget's x10 magnification. Biopsy on H&E stain of the vulva shows a section of the skin in keeping with typical Paget's cells with clearly demarcated abundant pale cytoplasm containing mucin, scattered within the epidermis.

Figure 2 Urethral Paget's x40 magnification. Biopsy on H&E stain of the urethra shows a section of the urethral squamous mucosa with Paget's cells and pagetoid involvement of the urethral mucosa in keeping with vulval extramammary Paget's disease with extension involving the bladder and urethra.

EMPD was first described by Sir James Paget in 1874,¹ and the first case of EMPD of the vulva was reported in 1901.² EMPD of the vulva is a rare intraepithelial adenocarcinoma-in-situ originating in the apocrine sweat glands with Paget's cells found in sites other than the skin of the breast such as the genital regions (labia majora, scrotum, and perianal skin). The most frequently associated carcinomas are apocrine. Vulval EMPD most commonly occurs in postmenopausal women in their 50s and clinically presents with pruritus and soreness. The lesion typically presents as a pink eczematous-like lesion with white islands of hyperkeratosis and/or red, flaky, weeping patches.^{3–6} Patients may also be asymptomatic or present with pain, bleeding and chronic itching after several unsuccessful attempts of moisturisers and topical steroid creams with minimal response. Diagnosis is made by skin biopsy and or immunohistochemistry staining of GCDFP-15, CK-7, CK-20 and CEA. Pathologically, EMPD of the vulva resembles mammary Paget's of the nipple and areola.^{7,8}

Other factors associated with EMPD of the vulva include caucasian race, genetic predisposition, previous radiation exposure, increased body mass index and history of hormone replacement therapy.⁹

Patients with EMPD of the vulva are at increased risk of synchronous or metachronous neoplasms including cervical, colorectal, and transitional epithelium carcinomas.^{7,8,10} Therefore, routine

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screening in some cases and prolonged surveillance has been recommended, although there are no clear guidelines. Recommended screening tests to rule out co-existing malignancies include, colonoscopy, cervical cytology, mammogram, cystoscopy, and/or urinary cytology to rule out coexisting or underlying malignancies.⁷⁻¹⁰

Differential diagnoses of vulval EMPD includes psoriasis, lichen simplex chronicus/sclerosus/planus, differentiated vulval intraepithelial neoplasia, squamous cell carcinoma, histiocytosis, condylomata acuminata and melanoma.¹¹

Prognosis is favourable if the lesion is localised to epidermis but poor with invasion to dermis. First line treatment includes vulvectomy and/or wide local excision with wide margins up to 1.5–2 cm away from visible lesion.

Recurrence rate after surgical excision is reportedly 32%¹² and up to 50%–70% of lesions will have positive resection margins.^{7,9,13} Paget's has also been treated with Imiquimod cream or Cidofovir, radiotherapy, laser and photodynamic therapy in isolated cases. A small percentage (10%–20%) carry an underlying malignancy. Primary origin is skin and secondary adjacent regions may extend from the urethra, cervix, bladder,^{4,14-17} breast and bowel.

An option for treatment in this case would have been to proceed with surgery, but this would have involved an extensive resection with cystourethrectomy, and ileal conduits. Radiotherapy is sometimes treatment of choice in cases of postsurgical recurrence. Combination treatment with inclusion of chemotherapy has shown no clear benefit. Outcomes with wide local excision pose significantly longer survival rates versus radical interventions.^{4,9} Yet, alternative therapies such as medical management of Imiquimod remain unclear and controversial as some studies showed a positive clinical response with recurrent EMPD of the vulva.^{7,18}

Recently, a specific urothelial marker, GATA-3, classified as highly sensitive and specific for urothelial and breast carcinomas failed to differentiate between primary vulval Paget's disease from pagetoid urothelial intraepithelial neoplasia.¹⁹

Learning points

- Primary treatment for Paget's disease of the vulva remains surgery, though alternative therapies exist and the optimal management currently remains unclear.^{6,7,18}
- Patients with extramammary Paget's disease (EMPD) of the vulva are at increased risk of concomitant or metachronous neoplasms and routine screening and surveillance (colonoscopy, cervical cytology, mammography and cystoscopy) should be considered.⁶⁻¹⁰
- EMPD of the vulva is difficult to treat for surgeons as majority of patients will have multiple recurrences.^{7,9,12}

Contributors AM: Conception/design/acquisition data/interpretation data/original drafting and revision of manuscript/responsible for accuracy and integrity of work. AI: Patient care/conception/design/ manuscript revisions/final approval/accountable for all aspects of work. JL: Patient care/conception/design/ manuscript revisions/final approval/accountable for all aspects of work. LM: Patient care/conception/design/ manuscript revisions/final approval/accountable for all aspects of work.

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