

Case Report

Extramammary Paget's disease of the glans penis secondary to urethral recurrence of bladder carcinoma after radical cystectomy: A case report

Ryoma Nishikawa,¹  Masashi Honda,¹ Toshihiko Masago,² Shuichi Morizane,¹ Katsuya Hikita¹ and Atsushi Takenaka¹

¹Department of Urology, Tottori University Faculty of Medicine, and ²Department of Urology, Yonago Medical Center, Yonago, Tottori, Japan

Abbreviations & Acronyms

CIS = carcinoma *in situ*
 CK = cytokeratin
 EMPD = extramammary Paget's disease
 GCDFP-15 = gross cystic disease fluid protein 15
 UC = urothelial carcinoma
 UP-III = uroplakin-III
 VPD = vulvar Paget's disease

Correspondence: Masashi Honda M.D., Ph.D., Department of Urology, Tottori University Faculty of Medicine, 36-1 Nishi, Yonago, Tottori 683-8504, Japan. Email: honda@tottori-u.ac.jp

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Introduction: Extramammary Paget's disease of the vulva secondary to urothelial carcinoma is rare. It is important to determine whether extramammary Paget's disease is primary or secondary, because the appropriate treatment strategies differ. We report a case of penile extramammary Paget's disease secondary to urothelial carcinoma recurrence.

Case presentation: A 75-year-old man who was diagnosed with bladder carcinoma and received urethra-sparing radical cystectomy 5 years ago presented with erythema and red spots in the glans penis. Immunostaining (cytokeratin 7 and cytokeratin 20) of skin biopsy specimens suggested a secondary extramammary Paget's disease that originated from the urothelial carcinoma. Under urethroscopy, urethral recurrence was also suspected. A total penectomy was performed, and a final diagnosis of urothelial carcinoma recurrence and secondary extramammary Paget's disease of the glans penis were established.

Conclusion: Using immunostaining, the differential diagnosis between primary and secondary extramammary Paget's disease is more accurate. Secondary extramammary Paget's disease should be considered when a skin lesion is present on the penis of patients with urothelial carcinoma.

Key words: bladder neoplasms, extramammary Paget's disease, penectomy, penis, urethral neoplasms.

Keynote message

EMPD of the glans penis secondary to urethral recurrence of bladder carcinoma is rare. It is difficult, but important, to diagnose whether EMPD is primary or secondary to UC, since the appropriate treatment strategies differ. Immunostaining improves the accuracy of the differential diagnosis. Secondary EMPD should be considered when skin lesions are present on the penis of patients with UC.

Introduction

EMPD was initially reported by Crocker,¹ who observed lesions on the penis and scrotum with histological features similar to those described in a previous report on the disease.² EMPD involves lesions that are similar to the symptoms of Paget's disease of the breast, occur outside the mammary gland, and are commonly found in the anogenital region. Such lesions can also develop on any skin or mucosal surface rich in apocrine glands, such as the axilla.

EMPD is classified as primary or secondary. Primary EMPD is thought to originate from intraepidermal cells or apocrine glands, while secondary EMPD is associated with internal

malignancies. We report a patient with EMPD of the glans penis, secondary to urethral recurrence of the bladder carcinoma, after radical cystectomy.

Case presentation

In March 2016, a 75-year-old man with a history of radical cystectomy and cutaneous ureterostomy for UC of the bladder (G3 > G2, pTis) 5 years previously, presented with erythema and red spots around the external urethral orifice (Fig. 1). At the first transurethral resection of bladder tumor in October 2011, UC was not detected from the urethra; hence, urinary diversion was initially planned for neobladder reconstruction. When the radical cystectomy was performed, malignant cells were detected from the left ureteral stump by rapid intraoperative pathological diagnosis, and two additional resections resulted in CIS or dysplasia; hence, urinary diversion was changed to cutaneous ureterostomy. No malignant cells were detected from the right ureteral stump. The length of the ureter was insufficient because the left ureter had to be excised twice additionally, and a stoma was created on the left side of the navel. Urethral resection was not performed because the urethral stump was negative. The resected margin of the specimen was negative except for the left ureteral stump. After surgery, bacillus Calmette-Guérin perfusion was performed six times in the left ureter, and no recurrence of bladder carcinoma in the upper urinary tract was observed. Postoperative urethroscopy was performed regularly and no recurrence of carcinoma was detected from the urethra.

Initially, he was treated with external medicine, but the lesion failed to improve. In June 2016, urethroscopy showed red spots on the urethra, without any tumors (Fig. 2). A skin biopsy of the glans penis was performed to obtain a histopathological diagnosis of secondary penile EMPD that originated from UC. Immunostaining revealed CK7-positive and CK20-positive (Fig. 3) results. Chest abdominal computed tomography showed no lymph node metastases.

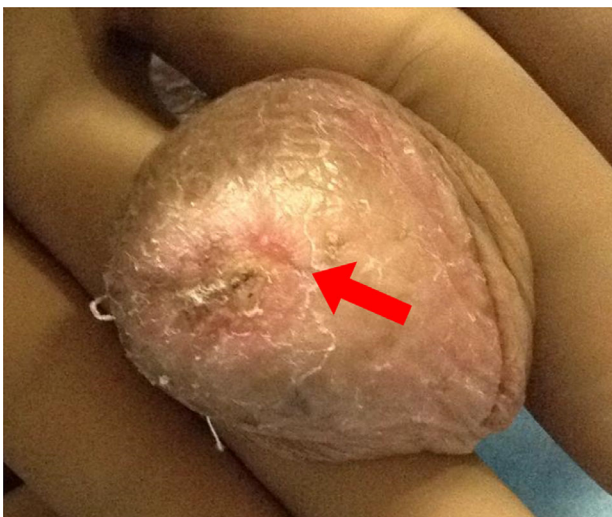


Fig. 1 Glans penis skin findings. Presentation of erythema and red spots around the external orifice.

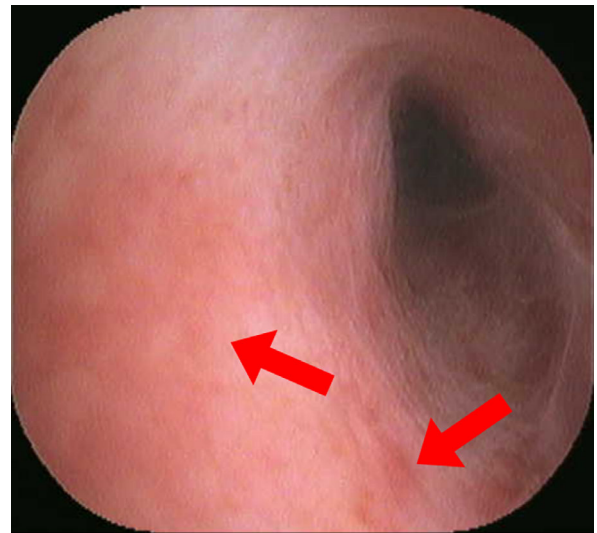


Fig. 2 Endoscopic findings of the urethra. In the urethroscopy, there were red spots on parts of the urethra.

We suspected that the patient had a urethral recurrence of bladder carcinoma and that the recurrence had infiltrated the glans penis, with pagetoid phenomenon. In November 2016, he underwent a total penectomy. The operation time was 124 min, and estimated blood loss was 30 mL. The patient's postoperative course was uneventful, and he left the hospital on the 11th postoperative day.

Histopathological findings of the resected specimen revealed UC recurrence (G3, pTis) on the urethra. Consistent with biopsy results, the histopathological findings supported the diagnosis of the glans penis, and the patient was diagnosed with Paget's disease progression to the glans penis (Fig. 4). The resection margin was negative, and the patient remained recurrence-free during follow-ups.

Discussion

EMPD of the vulva (VPD) is a rare intraepithelial lesion that accounts for 1–5% of vulvar neoplasms.³ The most common symptom of EMPD is pruritus with red macular lesions, and EMPD sometimes shows hyperpigmentation or hypopigmentation.⁴ In the anogenital region, atypical appearances can occur, such as ulceration or leukoplakia. The features can be nonspecific; and therefore, the disease is commonly misdiagnosed as an inflammatory or skin infection (eczema, psoriasis). As such, the lesions can advance due to inappropriate treatment.⁵ Our patient was initially treated using external medicine only.

EMPD is a cutaneous malignancy that is characterized by the growth of bright atypical cells, known as Paget's cells, in sites other than the breast skin such as the vulva, axilla, and the perianal region. Chanda reported that 12% of patients with EMPD have underlying concurrent internal malignancies,⁶ and there could be a strong association between the anatomic site of EMPD and the anatomic location of the internal malignancy. Therefore, patients with EMPD should be assessed for malignant diseases.

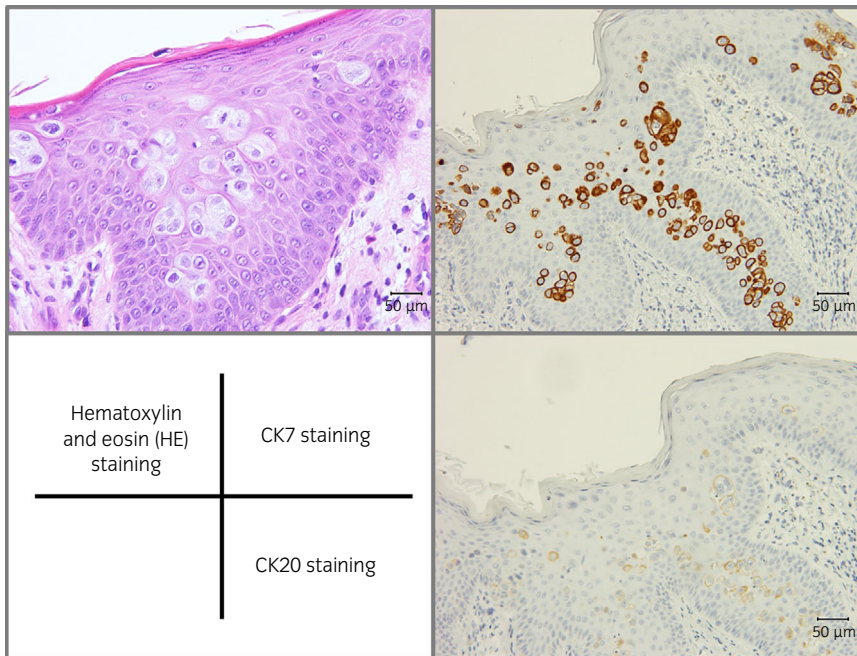


Fig. 3 Skin biopsy of the glans penis. Heterotypic cells with clear cells proliferated in the alveolar form in the epithelium. The cells were CK7 and CK20 positive.

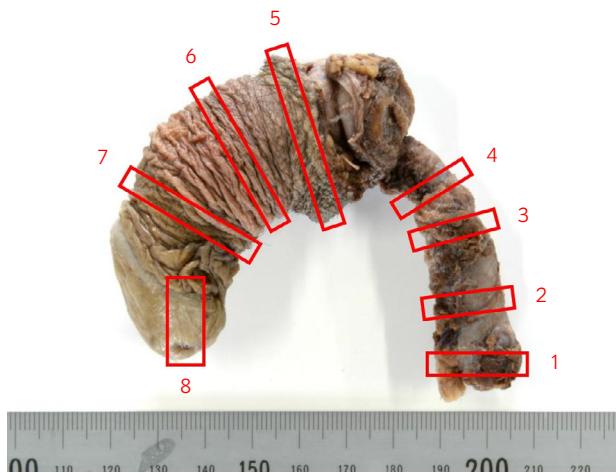


Fig. 4 The resected specimen. The histopathological examination showed UC in numbers three to seven (urethra) in the photograph, and progression of Paget's disease was detected in number eight (glans penis). There was no malignancy in numbers one and two, and the resected margin was negative.

For the differential diagnosis between primary and secondary EMPD, immunohistological analysis is useful. It has been reported that CK7, CK20, and GCDFP-15 staining are generally used for the differential diagnosis between primary and secondary EMPD.^{7–9} In our case, although GCDFP-15 was not assessed, the patient's condition was considered to be consistent with secondary EMPD, since both CK7 and CK20 staining were positive. Brown and Wilkinson¹⁰ and Yanai *et al.*¹¹ reported that UP-III, which is specific for urothelium, and p63, which is a member of the p53 tumor suppressor gene family, is expressed in normal urothelial cells and are only immunoreactive in secondary VPD of UC (VPD-UC). Therefore, both are useful markers for the

differential diagnosis between primary VPD and secondary VPD-UC. Conversely, Morbeck *et al.*¹² reported that GATA3, a specific urothelial marker, was not useful for differentiating between primary VPD and secondary VPD-UC because all 13 EMPD patients assessed had GATA3-positive results. According to these reports, primary VPD is generally CK7⁺/CK20⁻/GCDFP-15⁺/UP-III⁻/p63⁻ while secondary VPD-UC is CK7⁺/CK20⁺/GCDFP-15⁻/UP-III⁺/p63⁺.

The differentiation of primary and secondary EMPD in biopsy specimens is clinically important for guiding surgical treatment.¹³ The extent of surgical excision depends on whether EMPD is primary or secondary. In primary EMPD, the tumor is resected with a 1–3 cm surgical margin, for total layer resection on the fascia, due to progression into layers deeper than the dermis, or the progression of adenocarcinoma into layers below the lesion, in approximately 20% patients.¹⁴ However, for secondary EMPD, primary tumor treatment is performed in addition to skin lesion resection. Although the surgical margin is the same as that in primary EMPD, partial resection of the fat layer should be performed, because it is rare for the tumor to infiltrate deeper than the dermis.

In our case, extensive resection was performed because the patient had a urethral recurrence of bladder carcinoma along with secondary VPD-UC penile lesion. Therefore, total penectomy was performed.

Previously, only 13 cases of secondary penile EMPD of UC have been reported with a condition similar to that of this patient.^{15–18} In 12–16% of patients with CIS of the bladder, the pagetoid phenomenon was observed.^{19,20} This patient had a UC recurrence with CIS; therefore, CIS recurrence in the urethra may have caused the pagetoid phenomenon that infiltrated to the glans penis.

Thus, VPD can be easily misidentified as eczema or infection; however, patients with histories of urinary tract malignancies with skin symptoms of the vulva should be considered for the possibility of secondary VPD-UC.

Conflict of interest

The authors declare no conflict of interest.

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