Bladder Metastasis of Extramammary Paget’s Disease: A Case Report

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Extramammary Paget’s disease (EMPD) is a cutaneous malignancy which is characterized by growth of Paget’s cells in anatomical sites other than breast skin. The areas of predilection for the disease are usually vulva, axilla, and the perianal region. Bladder metastasis is very rare, because metastasis most commonly occurs in lymph nodes. Here we show a rare case of bladder metastasis of EMPD of the vulva. A 77-year-old man was referred to our hospital with erosion of the penis. Surgical resection was performed as a treatment under the diagnosis of EMPD. One year later, an abdominal CT showed a left hydronephrosis and thickening of the bladder wall, where cystoscopy revealed irregular mucosa on the left side of the bladder wall. Pathologic examination with immunohistochemical stains of bladder mucosa showed bladder metastasis of Paget’s disease of the vulva. Occasionally, the Paget phenomenon is observed from the external urethral orifice to the vulva in transitional cell carcinoma of bladder. Paget phenomenon and EMPD are histochemically and symptomatically very similar, and differentiation between the two is essential. CK20 and GCDFP-15 staining are used for such differentiation, and pathologic examinations of immunohistochemical stains effectively diagnose EMPD.

Key words: Extramammary Paget’s disease, bladder metastasis, immunohistochemical stains, CK20, GCDFP-15

Introduction

EMPD (EMPD) is a skin cancer of apocrine sweat gland origin. Prognosis is generally favorable, if tumors are localized in the epidermis. However, some cases have poor prognosis, if tumors invade the dermis. Metastasis to regional lymph nodes and skin is often observed in poor prognosis cases, but metastasis to the bladder is extremely rare. Here, we introduce a case report of hydronephrosis caused by bladder metastasis of EMPD from the genital area.

Case report

A 77-year-old man noticed penile erosion and consulted a dermatologist on August 20, 2008. The erosions spread from the left side of the base of the penis to the scrotum. A skin biopsy was followed by a pathologic diagnosis of EMPD (Figure-1). Because tumors had spread beyond the basal layer, resection of genital skin malignant tumor and split-thickness skin grafting were performed. The left inguinal lymph nodes were dissected, because of positive finding as rapid pathologic diagnosis during surgery. After the operation, pathological diagnosis with immunohistochemical stains showed the tumors to be CK20-negative, CK7-positive, GCDFP-15-positive, CEA-positive and there were tumors in lymph duct.

On July 21, 2009, the patient was referred to our
department because of high fever due to a complex urinary tract infection with right ureteral calculi. The results of our initial examination are as follows. Blood test: WBC 9.200/μl, Hb 12.3 g/ml, BUN 26 mg/dl, Cre 1.19 mg/dl, CRP 16.9 mg/dl. Urinary sediment: WBC myriad/hpf, RBC 16-20/hpf. An abdominal CT showed a ureteral calculus of 9 mm in the right middle ureter and right hydronephrosis, as well as increased fat concentration around the kidney (Figure-2). The patient was diagnosed with pyelonephritis and treated with antibiotics. We initially recommended a transurethral ureterolithotomy (TUL) for the right ureteral calculi. However, we ultimately chose conservative observation because the patients rejected the operation. We observed disappearance of right hydronephrosis via CT in October 2009; however, ureteral calculus remained in the vesicoureteral junction. At that
time, the patient’s lower left leg was observed to be edematous. Although locality of the ureteral calculus remained unchanged, December 2009 CT observation newly revealed left hydronephrosis and thickening of the left side of the bladder wall, where cystoscopy revealed irregular mucosa. The patient was admitted for further examination of this bladder tumor. The following data were obtained upon admission. Blood test: WBC 5,800/μl, Hb 12.5 g/ml, BUN 29 mg/dl, Cre 1.88 mg/dl, CRP 0.1 mg/dl, CEA 1.5 ng/ml, PSA 5.55 ng/ml. Urinary sediment: WBC 1–5/hpf, RBC 1–5/hpf. Urinary cytology: class V. An abdominal CT showed left hydronephrosis, left bladder wall thickening, right ureteral calculus, enlarged prostate and rise of fat concentration in lower abdominal skin. An abdominal MRI showed a bladder tumor, which invaded the muscle layer of the left side of the bladder wall (Figure-3), and left sacrum metastasis was suspected. There were no findings of the direct invasion from CT and MRI.

On January 22, 2010, transurethral resection of the bladder tumor was performed on the irregular bladder mucosa. Around the left ureteral orifice in the bladder, only edematous change was found. Pathological diagnosis revealed that the bladder tumor was carcinoma that was characterized by cord-like to solid infiltrating growth cells. Tumor cells had rich cytoplasm and a large oval, eccentric nucleus with a single large nucleolus. Some cells had foamy cytoplasm. Tumor cells located in the subepithelial layer and invaded into the muscle layer of the bladder (Figure-4). Pathological diagnosis with immunohistochemical stains showed the tumors to be CK20-negative, CK7-positive, GCDFP-15-positive (Figure-5) and CEA-positive. Finally, the patient was diagnosed with bladder metastasis of EMPD. Although we had planned to perform left ureteral stenting and right TUL, the patient suddenly developed bacterial meningitis and underwent palliative left nephrostomy. After palliative radiotherapy (total 30Gy) for bladder tumor treatment, we discovered multiple metastases to the scrotum, left groin, left popliteal and right inguinal skin, and performed radiation treatment on each. Eventually, multiple skin metastases, liver metastasis and multiple bone metastases were revealed, and we subsequently focused on the best possible supportive care. The patient died from carcinomatous pleurisy in April 2010.

Discussion

EMPD is a cutaneous malignancy, which is characterized by growth of bright atypical cells known as Paget’s cells in sites other than breast skin. The areas of predilection for the disease are

![Figure 4: Bladder tumor X200 HE; Tumor cells located in the subepithelial layer and invaded into the muscle layer. Bladder tumor cell is the same histology as genital skin tumor.](image)

![Figure 5: Bladder tumor Immunohistochemical study](image)  
5a. X200 CK20; negative for tumor cells  
5b. X200 CK7; positive for tumor cells  
5c. X200 GCDFP-15; positive for tumor cells
vulva, axilla, and the perianal region. It sometime leads to metastasis to other organs such as the lymph nodes. Adenocarcinoma of the rectum, anus, or bladder which spreads to the vulva or anal skin is known as Paget’s phenomenon. As Paget’s phenomenon and EMPD are both characterized by the growth of Paget-like cells in epidermis, it is very important to distinguish them carefully.

Immunohistochemical analysis is effective for the pathological diagnosis of EMPD. CK20 and GCDFP–15 staining are used for differential diagnosis between EMPD and the Paget phenomenon. Occasionally, the Paget phenomenon is observed from the external urethral orifice to the vulva in transitional cell carcinoma of bladder. Gastrointestinal epithelium, bladder epithelium, and Merkel cells are all CK20 positive, as are gastrointestinal adenocarcinoma, bladder transitional cell carcinoma, and Merkel cell carcinoma. Apocrine sweat glands (axilla, vulva, eyelid and ear canal), breast tissue with apocrine metaplasia, salivary glands (submandibular gland), parotid gland and bronchial submucosa are all GCDFP–15 positive. Tumor of esophagus, gastrointestinal tract, lung, liver, kidney, prostate, ovary and uterus are all GCDFP–15 negative. EMPD is CK20-negative / GCDFP–15-positive, whereas Paget phenomenon is CK20+/GCDFP–15-, characteristics seen in EMPD. In this case, skin and bladder tumors were CK20-/GCDFP–15+ and there were no findings of the direct invasion from CT and MRI. The patient was diagnosed with bladder metastasis of EMPD.

Radical treatment for EMPD is surgical resection. In cases in which lesions are limited to the epidermis, the latter are surgically removed at a level of subcutaneous fascia 3 cm or more apart with subcutaneous fat tissue from the lesion border. The possibility of cure by radical surgery is high in these cases. Cases involving lateral lymph node metastases can often result in radical cure by lymph node dissection. Cases with bilateral lymph node metastasis, however, often lead to distant metastasis in the early stages. If there are bladder metastases, urinary diversion and total cystectomy are also considered.

Radiotherapy is sometimes the treatment of choice in cases of post-surgical recurrence, unresectable cases, and when surgical removal is impossible due to the issue of remaining organ function. The radiotherapy survival rate is poor: about 20% with invasive cancer. Combination therapy with chemotherapy has also been tried in some cases but the benefit is not clear.

The efficacy of chemotherapy for advanced stage EMPD with distant metastasis is unknown. There are reports of EMPD treatment using a combination of anti–cancer agents utilized in cases of digestive organ cancer, adenocarcinoma, and breast cancer; however, it is unclear whether or not this can prolong survival.

Since EMPD tumor cells express the androgen receptor at a high rate, anti-androgen therapy is also a treatment candidate. In addition, over–expression of erb–2 is reportedly detected in about 20% of EMPD; in such cases, combination therapy with trastuzumab and anti–cancer agents would be effective. As the above examples reflect only a few cases, expansion of case study reports is needed for verification of treatment efficacy.

In our own case study, the patient suffered both from hydronephrosis, due to right ureteral orifice invasion of bladder metastasis, and left ureteral calculi, which caused post-renal failure. Our initial plan to perform left urethral stenting and right TUL was replaced by palliative left nephrostomy, as the patient unexpectedly developed bacterial meningitis. Local radiotherapy was performed for treatment of bladder tumors. The patient had no metastasis in other organs, but his general condition was not good enough to undergo total cystectomy and urinary diversion. As he also had renal insufficiency, he could not receive chemotherapy.

There is a report of total cystectomy and urinary diversion for a case of bilateral hydronephrosis with bladder metastasis of EMPD. However, the case unfortunately resulted in postoperative mesenteric thrombosis. It is reported that EMPD is more prevalent in the elderly, and that about 15% of such patients have malignant tumors of other organs. This fact complicates indications for surgery.

**Conclusion**

We report here an extremely rare case of bladder metastasis of EMPD. There are some cases leading to Paget phenomenon on vulva in bladder transitional cell carcinoma which urologists observe in daily medical practice. Histopathological alteration...
and clinical course in both Paget phenomenon and primary cutaneous EMPD are very similar. As both treatment choice and prognosis differ significantly, however, a clarified differential diagnosis is key. Cooperation with the relevant pathologist is important for diagnosis.

Reference