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Case Report

Testicular metastasis of bladder urothelial carcinoma: a case report and related factors

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Abstract: Objective: The goal of this rare case report was to investigate potential factors that could contribute to testicular metastasis of bladder urothelial carcinoma. Methods: A retrospective analysis of the clinical data of a male patient who had a left testicular metastasis of bladder urothelial carcinoma after transurethral resection of bladder tumour and a series of chemotherapy in our hospital and review of related literature. Result: The patient was treated with left testicular radical resection, followed by confirmation of the disease with immunohistochemistry and pathology. After follow-up for 8 months, the patient died of systemic metastasis. Conclusion: Testicular metastasis of bladder urothelial carcinoma is very rare and it is more likely to occur on patients with older age, prostate metastasis and chemotherapy history. Especially, repeated bladder irrigation, transurethral surgery, high-tension bladder, and long-term chemotherapy are significantly associated with this rare case.

Keywords: Metastatic testicular carcinoma, urothelial carcinoma, secondary testicular cancer

Introduction

Bladder cancer is the most common tumour of the urinary tract and the morbidity is ranked 11th of worldwide malignant tumors [1]. The main risk factors are environmental exposure such as smoking and occupational exposure to chemicals used in the dye, rubber, leather, and painting industries. It is more likely observed in males than in females (ratio: 3.5:1) [2]. In terms of distant metastasis, liver is the most commonly detected organ, followed by lung, bone marrow, and adrenal gland [3]. Cases of testicular metastasis are very rare and are usually discovered by autopsy [4-6]. Following we report the diagnosis and treatment of a case of testicular metastasis of bladder urothelial carcinoma in our hospital and investigate the related factors.

Case report

A 75-year-old male first presented at a local community hospital in August 2014 due to a progressive dysuria without gross hematuria. As benign prostatic hyperplasia (BPH) was primarily diagnosis, surgery was prepared for transurethral resection of the prostate (TURP). Intraoperatively, trigone inflammatory edema indicated trigonitis and a 3 cm×3 cm-in-size cauliflower-like mass located on the right bladder wall was suggestive of a tumor. Then transurethral resection of the tumor and prostate was performed. Postoperative pathological report confirmed urothelial carcinoma (**Figure 1A**) with prostatic involvement (**Figure 1B-E**) (T4, high grade). Routine postoperative intravesical chemotherapy with mitomycin and cystoscopy showed no evidence of tumour recurrence.

Until December 2014, regular follow-up with cystoscopy showed a mucosa lump which was adjacent to right ureter. Histology of the detected lump indicated transitional epithelial carcinoma (high grade). The patient complained a 2-month painful and swollen left scrotum. Scrotal ultrasound scan revealed a 22 mm no-echo hard mass in left epididymal without testicular tumour. Diagnosis of bladder cancer, hydrocele of testis and epididymitis were then made. In this case, radical cystectomy with pel-

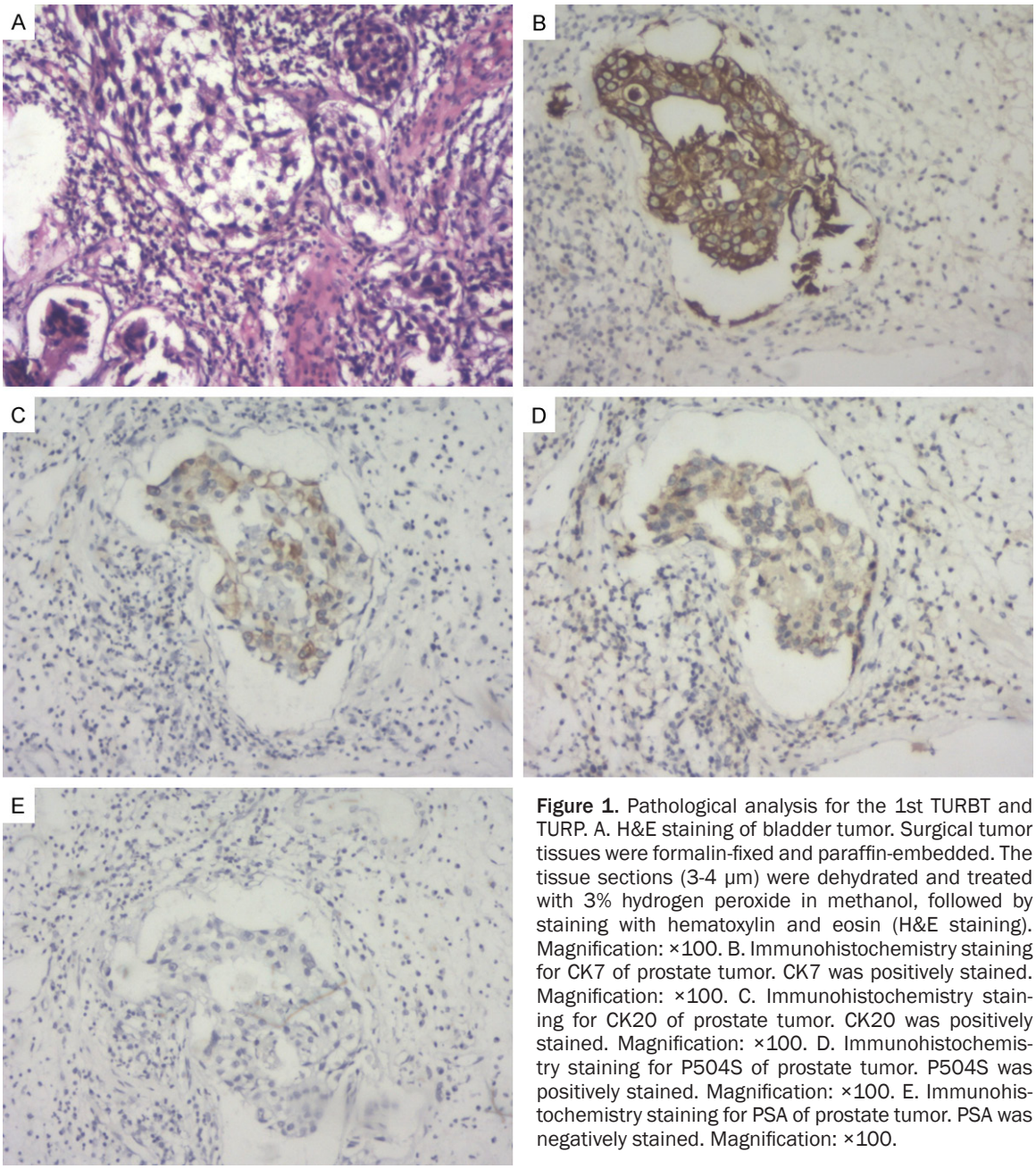

Figure 1. Pathological analysis for the 1st TURBT and TURP. A. H&E staining of bladder tumor. Surgical tumor tissues were formalin-fixed and paraffin-embedded. The tissue sections (3-4 μm) were dehydrated and treated with 3% hydrogen peroxide in methanol, followed by staining with hematoxylin and eosin (H&E staining). Magnification: ×100. B. Immunohistochemistry staining for CK7 of prostate tumor. CK7 was positively stained. Magnification: ×100. C. Immunohistochemistry staining for CK20 of prostate tumor. CK20 was positively stained. Magnification: ×100. D. Immunohistochemistry staining for P504S of prostate tumor. P504S was positively stained. Magnification: ×100. E. Immunohistochemistry staining for PSA of prostate tumor. PSA was negatively stained. Magnification: ×100.

vic lymph node dissection was performed. However, due to advanced age, low score in preoperative scoring system and left lung radical resection history, radical cystectomy was unbearable to the patient. So diagnostic transurethral resection of bladder tumor (TURBT) was performed followed by epididymal anti-inflammatory treatment. Postoperative histology indicated an invasive papillary transitional epithelial carcinoma, high grade with vessel involvement.

After 3 courses of systemic chemotherapy with gemcitabine and 7 times of intravesical chemotherapy with mitomycin, the patient was, for the third time, administrated for gradually enlarged and painful left testis in June 2015. Examination revealed a roughly 8 cm-in-size, hard, irregular testicular mass which was highly suggestive of a testicular neoplasm. Exploratory surgery for the left testis was performed. Operative observation confirmed a hard, rough, adhesive, and enlarged left testis, therefore left testis radical

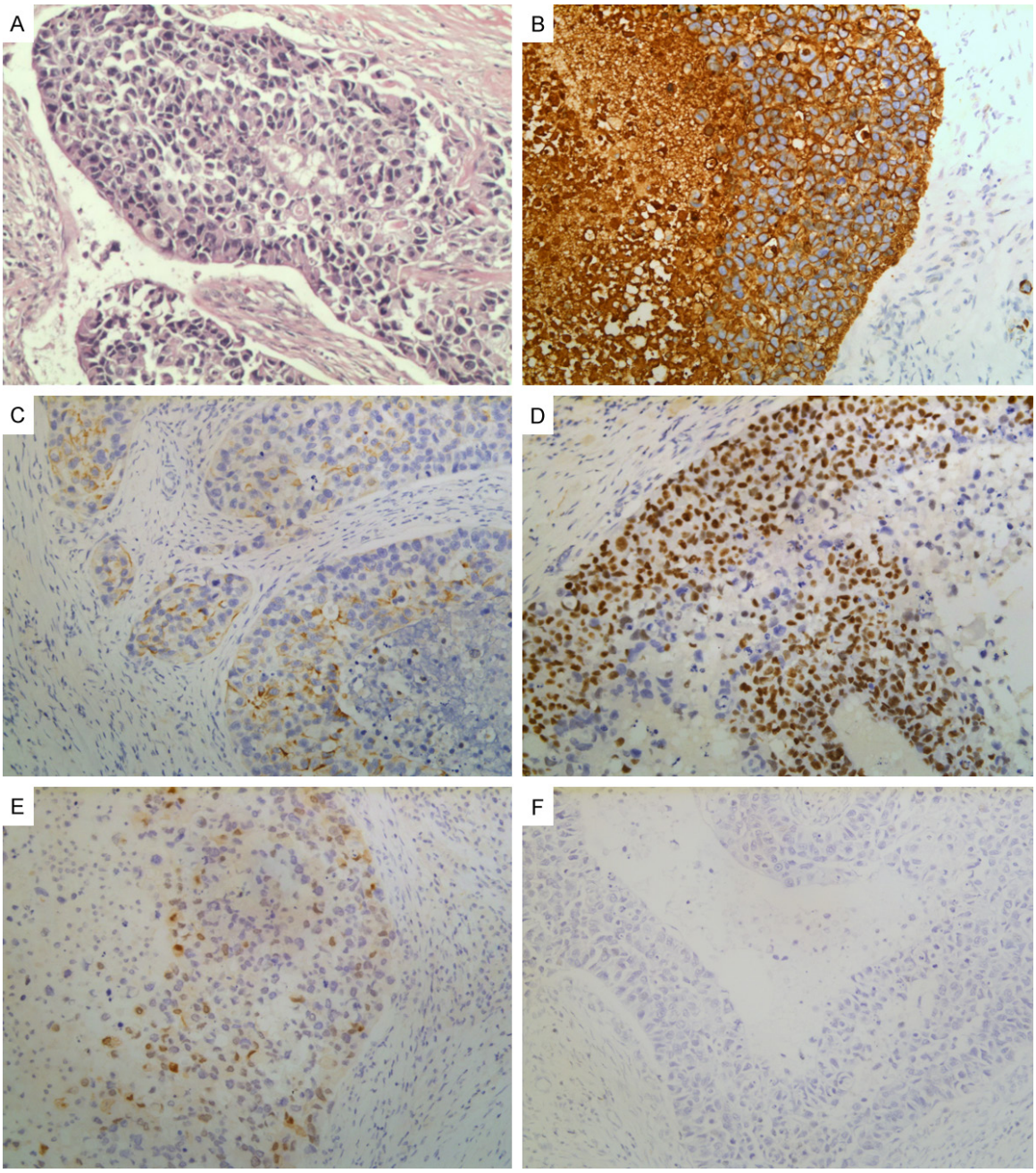

Figure 2. Pathological analysis for the left testis radical resection. A. H&E staining of testicular tumor. Magnification: ×200. B. Immunohistochemistry staining for CK7 of testicular tumor. CK7 was positively stained. Magnification: ×200. C. Immunohistochemistry staining for CK20 of testicular tumor. CK20 was focal positively stained. Magnification: ×200. D. Immunohistochemistry staining for P63 of testicular tumor. P63 was positively stained. Magnification: ×200. E. Immunohistochemistry staining for Oct3/4 of testicular tumour. Oct3/4 was focal positively stained. Magnification: ×200. F. Immunohistochemistry staining for PLAP of testicular tumor. PLAP was negatively stained. Magnification: ×200.

resection was instead. Postoperative pathology (**Figure 2A**) demonstrated a left testicular metastasis of bladder urothelial carcinoma with localized necrosis within the range of tunica albuginea testis. Multiple positive vesicular invasions were detected. While, neural, spermaduct and spermatic cord cutting margin were negative without invasion. Immunohistochemistry indicated (**Figure 2B-F**): CK20 (focal+), CK7(+), P40(+), P63(+), PLAP(-), Villin(-),

Oct3/4 (focal+). Follow-up for 8 months after the third operation was performed until the patient finally died of systemic metastasis.

Discussion

In China, bladder cancer is the 7th malignant tumor in males, which is lower when compared to Western countries. The incidence of bladder cancer remains rather low before age 45, while it becomes elevated gradually after age 45. The peak morbidity of the tumour in rural area can be observed at age 80 suggesting an age-advanced disease [7]. The main risk factors of bladder cancer include smoking and occupational exposure. Dyestuff manufacture, rubber chemical industry, pharmaceutical industry, pesticide, paint, leather, aluminum, and steel production field are considered to be highly carcinogenic [2, 7]. The most common clinical symptom of bladder cancer is painless, whole course, gross hematuria which accounts for 80%. Irritation sign of bladder and other signs of urinary tract obstruction contribute to the rest 20%. For advanced bladder cancer, the most common organ of metastasis is liver, followed by lung, bone marrow and adrenal gland [3]. Metastasizing malignant tumor to the testis could be originated from prostate, lung, gastrointestinal tract and kidney, but the case of metastasized from bladder urothelial cancer is very rare [8].

Possible pathogenic factors

According to the literature, testicular metastasis accounts for 0.9%-2.4% of all observed tumors in the testis [9]. A multi-center randomized autopsy cohort study demonstrated that the discovery rate of the metastatic tumour in testis was as low as 0.02% to 0.06% and fifty percent of the primary origins of these metastatic tumor were prostate and lung [9-11]. The bladder was exceptionally rare as the metastatic source. There were 948 cases confirmed of bladder cancer in our hospital during the recent 5 years and only one of them got his testis metastasized. Another 87-case autopsy based study found that metastasis of the bladder carcinoma tended to occur on the case whose prostate was involved. More specifically, the state that 21 out of 23 of the cases testified this result [12]. In our case, prostatic involvement was detected at the first TURP. These can be deemed as evidences to support the association between testicular metastasis of urothelial carcinoma and prostatic involvement.

Blood-testis barrier is one of the proven protective mechanism of the organism. It not only prevents large molecular substances from going into the seminiferous tubule via blood or lymphoid pathway, but also serves as an immune barrier. The existence of the barrier forges a solitary fortress for the testis preventing outer invaders. Therefore, the probability of testicular metastasis is extremely small. Aging could be an influencing factor, supported by an animal study [13]. The particular animal model indicated that there were many cellular connections in their testicular sertoli cells, however typical tight junctions were rare in old Brown Norway rats, which suggested the blood-testis barrier of an old rat was weak. Epidemiological investigation shows that the morbidity of bladder cancer climbs up gradually from age 45 due to aging factors [1].

Additional investigation showed that use of cyclophosphamide could make spermatogenic epithelium thinner, with the sertoli cells scattered in their distribution and the intercellular space expanded to suggest an impaired blood-testis barrier [14]. Some cytotoxic medications, like platinum-based drugs, have been proven to be destructive to blood-testis barrier. The healthy side of the testicular nonseminomatous germ cell tumor can obtain a 3 times higher probability of occurring tumor than expected after chemotherapy of platinum-based drug [15, 16]. These all confirm the association between systemic chemo-drugs and a damaged blood-testis barrier. The case we report also had a gemcitabine chemotherapy history before testicular metastasis was observed and post-operation histology demonstrated vascular invasion suggesting a hematogenous spread through blood-testis barrier was highly possible. However, there is no direct evidence supporting a role for gemcitabine in destroying the blood-testis barrier. Therefore, chemotherapy is one of the leading factors for testicular metastasis.

Mechanism of metastasis

A series of case reports conducted by Howard concludes that of testicular metastasis of bladder transitional cell carcinoma could be explained by the following pathways: 1. retro-

grade vein spread or embolism; 2. arterial embolism; 3. lymphatic metastasis; 4. seminiferous tubular dissemination [17]. While another case study proposed by Rafal prefers the theory that direct invasion from involved prostate would be the common spread way. In accordance to their theory, post-surgery histology normally shows seminiferous tubular involvement but vascular involvement is not frequently detected [18]. Dysfunction of the blood-testis barrier (gap junctional enlargement) due to chemotherapy facilitates dissemination of the neoplastic cells via blood [16]. There are no clear reports and explanations for other metastatic mechanisms.

In our case, the 75-year-old patient experienced recurrent transurethral procedures (recurrent intravesical perfusion, TURBT, urinary retention and so on) which allowed detached translational epithelial carcinoma cells to spread retrospectively through urinary tract. The first TURP demonstrated prostatic involvement, which was one possible mechanism discussed above. Systemic chemotherapy with gemcitabine followed by the second surgery (TURBT) may destroy the blood-testis barrier. Although there is no clear evidence saying that gemcitabine is threatening the blood-testis barrier, testicular metastasis may be led by hematogenous metastasis due to multiple vascular involvement shown on pathological sections. Missing points deserve more attention in future work: 1. no assessment for signs of metastasis in pelvic cavity after acknowledging the prostatic involvement; 2. when the left scrotum increased for the first time, only scrotum ultrasound was taken and further exploratory procedure for testis is ignored.

In summary, translational epithelial carcinoma derived from bladder detected as a secondary tumor in testis is exceptionally rare. Advanced age, prostatic involvement, and chemotherapy history are considered as related risk factors. In particular, patients with recurrent intravesical perfusion, TURBT, and urinary retention history combined with chemo treatment are highly suspected for testicular metastasis. Cautious attitude for iatrogenic dissemination of metastasis should be raised upon every transurethral operation and excessive operation should be constrained to the minimum.

Disclosure of conflict of interest

None.

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