Case Report

Testicular metastasis from urothelial carcinoma of the bladder

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Abbreviations & Acronyms
CT = computed tomography
Cx = chemotherapy
HoLEP = holmium laser enucleation of the prostate
N/R = not reported
Rx = radiotherapy
TUR-Bt = transurethral resection of the bladder tumor
UC = urothelial carcinoma

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Introduction: Reports of urothelial carcinoma with testicular metastasis are limited and the etiology and prognosis remain unclear. We report a rare case of testicular metastasis derived from bladder urothelial carcinoma.

Case presentation: A 68-year-old man presented with gross hematuria and urinary frequency. Cystoscopy demonstrated an 8-cm-sized tumor in the bladder; transurethral resection and magnetic resonance imaging confirmed invasive urothelial carcinoma. Cystoprostatourethrectomy was performed, and the pathological diagnosis was high-grade muscle-invasive urothelial carcinoma. Three years later, the patient noticed a left scrotal mass. Left high orchiectomy was performed, and histopathologic examination of the surgical specimen revealed urothelial carcinoma, confirming testicular metastasis derived from bladder cancer. The patient received chemotherapy with gemcitabine and cisplatin and has survived for 7 years since the initial diagnosis without progression.

Conclusion: Although rare, secondary lesions should be considered for the differential diagnosis of testicular tumors in patients with a history of urothelial carcinoma.

Key words: bladder cancer, metastasis, testicular tumor, transitional cell carcinoma, urothelial carcinoma.

Keynote message

Although metastatic bladder cancer is associated with a poor prognosis, studies of testicular lesions are limited to isolated case reports. Here, we report a rare case of metastatic bladder cancer to the testis with a review of published cases. Secondary lesions should be considered as a differential diagnosis of testicular tumors in patients with a history of bladder cancer.

Introduction

Based on the latest Global Cancer Observatory estimate for 2020, 570 000 people were newly diagnosed with bladder cancer, which is the 10th most common cancer worldwide.[1] The 5-year survival rate of patients with bladder cancer in the United States has been reported to be 77% for all stages, but is dramatically reduced to <5% in patients with distant metastasis.[2] This reflects the poor prognosis of metastatic bladder cancer, and the treatment strategy may be the key to reducing mortality. Although UC of the bladder (the most common histological type of bladder cancer, accounting for >90% of all cases of bladder cancer[3]) is known to spread to various organs, there have been few reports of cases of testicular metastasis, and the etiology and prognosis of this condition remain unclear. Here, we report a rare case of testicular metastasis derived from bladder UC.

Case presentation

A 68-year-old man with a history of HoLEP surgery presented with gross hematuria and urinary frequency. Cystoscopy demonstrated an 8-cm non-papillary solid tumor in the right wall of the bladder. He was an ex-smoker with no other risk factors or family history. Transurethral resection of the bladder tumor was performed, and histology revealed UC G3 pT1. Magnetic resonance imaging indicated possible muscle invasion (Fig. 1), and the patient

underwent cystoprostatourethrectomy and ileal conduit. The histological diagnosis was UC G3 pT2 with lymphatic and vascular invasion and in situ progression to the prostatic duct, but a negative surgical margin. No adjuvant treatment was administered. Six months after the surgery, the patient presented with a 2-cm tumor protruding from the meatus. Biopsy confirmed UC recurrence at the remnant urethral end. Partial penectomy and inguinal lymphadenectomy were performed. No positive tumor margin or metastasis to the lymph node was observed. Therefore, adjuvant chemotherapy was not administered. Regular biannual follow-up with CT had shown no evidence of tumor recurrence for 3 years after reoperation until the patient presented with a painless left testicular swelling. CT revealed a mass in the left testicle and right internal iliac lymphadenopathy (Fig. 2). Testicular tumor markers were negative. Left high orchiectomy was performed, and the histopathological diagnosis of the specimen (Fig. 3) was high-grade UC and confirmed testicular metastasis derived from bladder UC. The patient received six cycles of chemotherapy with gemcitabine and cisplatin, followed by eight cycles of maintenance chemotherapy with gemcitabine alone until it was suspended due to renal insufficiency. The target lesion of the pelvic lymph node shrank from 29 to 12 mm (short axis diameter), and the chemotherapy was evaluated as partial response according to Response Evaluation Criteria in Solid Tumors version 1.1.[4] The patient survived without regrowth of the pelvic lymph node at 7 years after diagnosis and 3 years after orchiectomy.

Discussion

Testicular tumors are relatively rare, and the National Cancer Institutes in the United States reported that the age-adjusted incidence of new cases of testicular cancer was 6.0 per 100 000 men per year, based on 2014–2018 estimates.[2] Of these, secondary testicular tumors (aside from leukemia and lymphoma) are extremely rare, accounting for 0.1–2.4% of all testicular tumors.[3] Common primary sites are the prostate, lungs, skin melanoma, colon, and kidneys, which account for approximately 80% of the primary sites.[5] Metastasis derived from bladder UC is seldom reported, with only 12 case reports identified in a literature review of PubMed from 1966 to the present (Table 1).[3,6–16] In all cases including ours, the median time from initial diagnosis to testicular metastasis was 2 years. Nine patients had histologically confirmed muscle-invasive bladder cancer, while only one patient had the other distant lesion before the testicular metastasis. Although only half of these case reports mentioned the outcome, five out of the seven cases reported that the patient survived.

Howard et al. discussed the metastatic pathways from the primary sites to the testicle: (i) retrograde lymphatic extension, (ii) retrograde venous extension, (iii) through the vas deferens lumen, (iv) arterial embolism, and (v) by continuity.[17] Hematogenous and lymphogenous spread can involve any site, and our case suggests the possibility of micrometastasis via these pathways based on the pathological findings. Some reports also indicate the possibility of intraluminal extension via the vas deferens.[3,9,14,15] Historically, bilateral vasectomy had been routinely carried out previously in transurethral surgery of the prostate in order to prevent acute epididymitis.[18] In addition, there have been case reports of tuberculous epididymitis after intravesical bacille Calmette–Guérin instillation therapy.[19] This indicated the possibility of regurgitation from the urinary tract to the seminal tract. Furthermore, of all previous case reports of testicular metastasis from UC of the bladder shown in Table 1, five patients had a previous history of transurethral surgery of the prostate, and five patients had confirmed prostate invasion before testicular metastasis. Our case also had a history of HoLEP, which may have opened the ejaculatory duct and allowed malignant

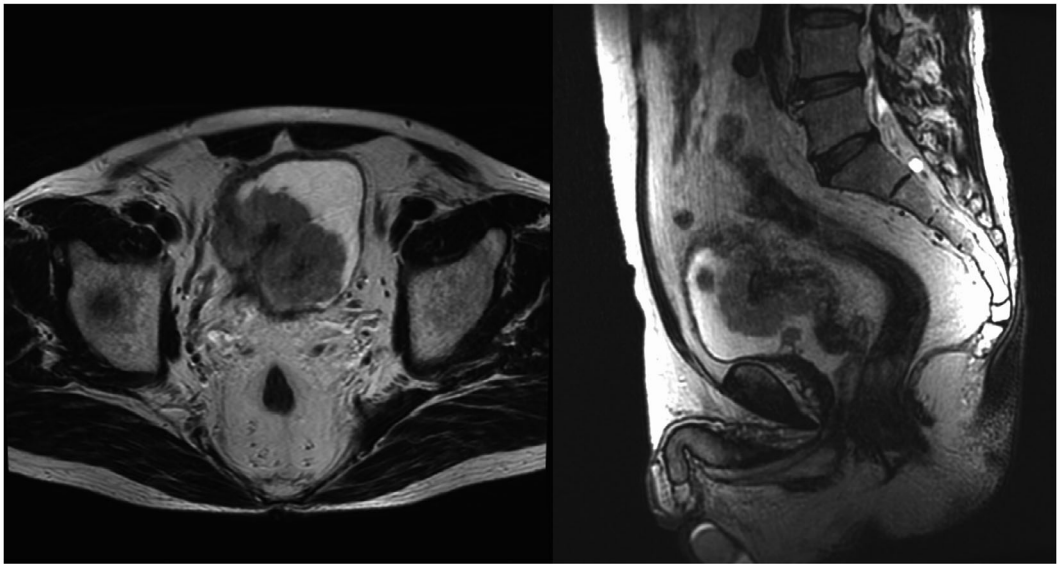

Fig. 1 Magnetic resonance imaging. Magnetic resonance image showing an 8-cm tumor at the posterior wall of the bladder, which suggested possible muscle-invasive bladder cancer.

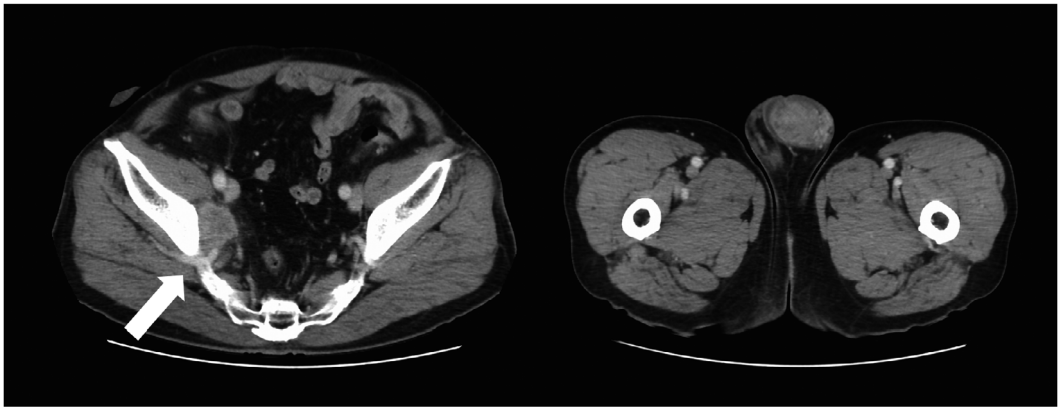

Fig. 2 Computed tomography. Computed tomography showing a mass in the left testicle as well as the right internal-iliac lymphadenopathy (arrow), suggesting metastatic spread of the bladder cancer.

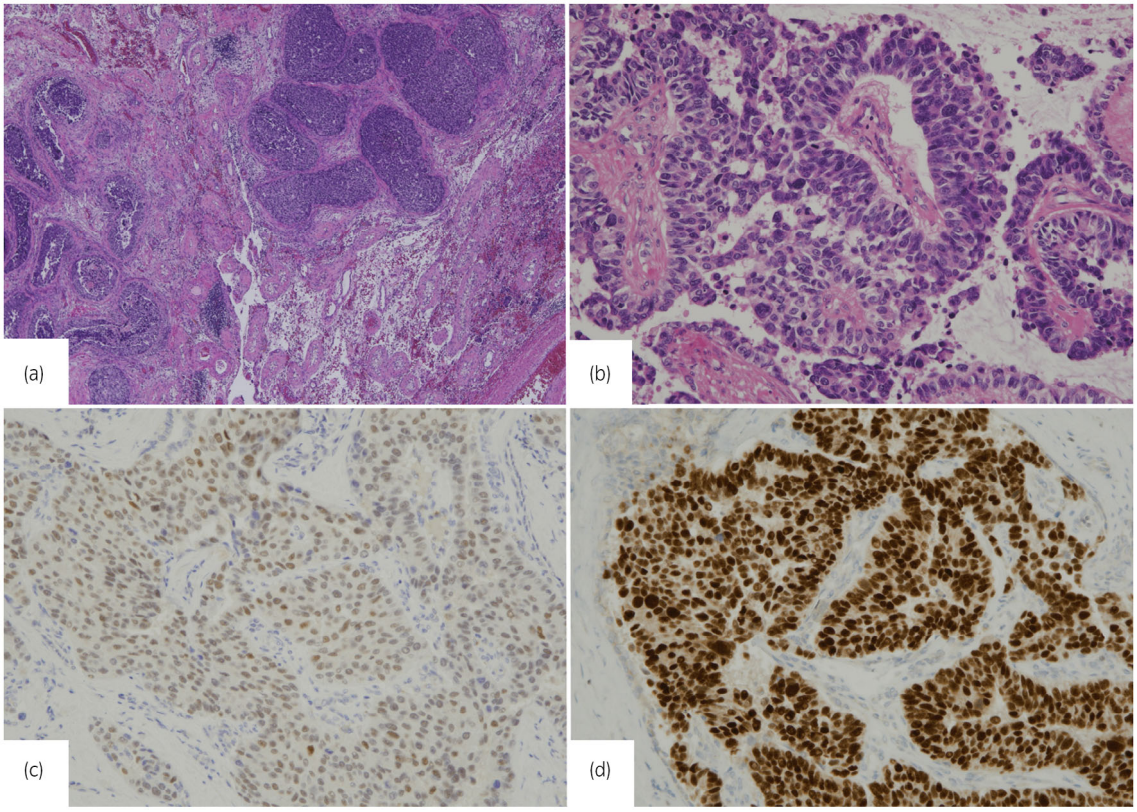

Fig. 3 Histology. Specimen of the testis exhibiting urothelial carcinoma infiltration. (a) Hematoxylin and eosin staining, 10× magnification, and (b) 2× magnification. The specimen was positive for (c) Uroplakin3 and (d) GATA3.

cells to penetrate retrogradely. We also found in situ progression of UC to the prostatic duct in the cystectomy specimen, as well as urethral recurrence, which may support the hypothesis above, although the surgical margin of the spermatic cord was negative for carcinoma. This pathway has a blind end, and it seems to have a somewhat different setting from that of the hematogenous and lymphogenous pathways, which circulate throughout the body. Further, testicular tumor may be anatomically easier to resect than those involving intracorporeal organs. Therefore, if a certain extent of testicular metastasis of bladder UC was due to intraluminal extension via the vas deferens, their prognostic determinants are likely to depend on the progressive capacity of bladder cancer except testicular metastasis at that time.

Our case achieved a relatively good outcome with surgery and chemotherapy despite the aggressiveness of the tumor. As information regarding the treatment outcome is scarce due to the extremely limited number of case reports, further accumulation of such cases is needed to determine the

Table 1 Characteristics of the previously reported cases of bladder urothelial carcinoma with testicular metastasis

No.	Author	Year	Age	Treatment before testicular metastasis					Tumor stage at diagnosis (metastatic sites)	Time from presentation to testicular metastasis	Laterality	Outcome
				TUR-P	TUR-Bt	Cystectomy	Rx	Cx				
1	Binkley WF, et al.[3]	1984	69	Yes	Yes	No	Yes	No	pTxN1M0 (Stage D1 disease)	8 months	Left	Died of disease; 8 months after orchiectomy
2	Oppng FC, et al.[6]	1991	67	No	Yes	No	Yes	No	pT1N0M0	2 years	Bilateral (asynchronous)	N/R
3	Doherty AP, et al.[7]	1996	64	No	Yes	Yes†	Yes	No	pT3NxMx	2 years	Bilateral (asynchronous)	N/R
4	Morgan K, et al.[8]	2004	74	Yes	Yes	Yes	No	No	G3, pT4aN0M0 (Prostate and base of the seminal vesicles invasion)	synchronous	Right	Survival; 1.5 years after adjuvant chemotherapy
5	Thwaini A, et al.[9]	2006	74	No	Yes	No	Yes	No	G2, pT3N0M0	3 years	Left	N/R
6	Mahmalji W, et al.[10]	2011	72	Yes	Yes	Yes	No	No	G2, pT4aN0M0 (Prostate invasion)	10 years	Left	Survival; unknown observation period
7	Nouhaud FX, et al.[11]	2012	58	No	Yes	No	No	No	G2, pTaNxMx	6 years	Left	Survival; unknown observation period
8	Kozak GN, et al.[12]	2012	84	Yes	Yes	No	No	No	pT1NxMx	1 year	Right	N/R
9	Kiely G. et al.[13]	2013	71	No	Yes	No	Yes	Yes	G3, pT2N0M1 (Lung metastasis)	1 year	Bilateral (asynchronous)	Died of disease; 2 years after initial presentation
10	Turo R, et al.[14]	2014	61	No	Yes	Yes	No	No	G3, pT4a (Prostate invasion)	2 years	Right	N/R
11	Ymir S. et al.[15]	2018	37	No	Yes	Yes	No	Yes	G3, pT4aN1 (Prostatic stroma and seminal vesicles invasion and internal iliac lymph node metastasis)	11 years	Left	N/R
12	Wu K. et al.[16]	2019	67	Yes	Yes	Yes	No	Yes	G3, pT4aN1M0 (Capsula prostatica and bilateral seminal vesicle invasion and right pelvic lymph node metastasis)	1 year	Right	Survival; 1 year after orchiectomy
13	Our case	2021	68	Yes	Yes	Yes	No	No	G3, pT2aN0M0	4 years	Left	Survival; 3 years after orchiectomy

†Simple cystectomy for persistent haematuria caused by radiation cystitis and not by recurrence of UC (confirmed histologically).

prognosis of testicular metastasis from UC of the urinary bladder.

Conclusions

Here, we report a rare case of testicular metastasis of bladder UC. Although rare, metastatic tumors should be considered in the differential diagnosis of testicular tumors in patients with a history of bladder UC.

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Author Contribution

Eri Fukagawa: Conceptualization; Data curation; Investigation; Project administration; Visualization; Writing-original draft; Writing-review & editing. Fumiyasu Endo: Conceptualization; Data curation; Project administration; Supervision. Yoko Kyono: Data curation; Writing-review & editing. Jun Hashimoto: Data curation; Writing-review & editing. Kazunori Hattori: Data curation; Supervision; Writing-review & editing.

Conflict of interest

The authors declare no conflict of interest.

Approval of the research protocol by an Institutional Reviewer Board

The protocol for this research project has been approved by a suitably constituted Ethics Committee of St. Luke's International Hospital (Approval No. 21-R045).

Informed consent

Informed consent was obtained from the subject.

Registry and the registration no. of the study/trial

Not applicable.

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Editorial Comment

Editorial Comment to Testicular metastasis from urothelial carcinoma of the bladder

Among the clinically organ-confined genitourinary malignancies, invasive bladder cancer is one of the most lethal diseases, nearly half of which recur even after radical surgery.[1] For the treatment of recurred metastatic urothelial cancer, therapy with the immune checkpoint inhibitor pembrolizumab is being rapidly introduced in clinical practice.[1] Enfortumab vedotin, which is a novel antibody drug conjugate anticancer agent, has also very recently been approved as a third-line standard medical therapy.[2] The most frequent visceral metastatic site from urothelial cancer is the lung, followed by the liver and bone. Testicular metastasis from bladder cancer is truly rare.

In this issue of *IJU Case Report*, Fukagawa *et al*. reported a case of testicular metastasis from urothelial cancer of the urinary bladder in a patient with a history of holmium laser enucleation of the prostate (HoLEP) for benign prostate hyperplasia and partial penectomy for urethral cancer recurrence after radical cystoprostatectomy.[3] Three years after the partial penectomy, the patient presented with painless left testicular swelling.[3] He underwent left high orchiectomy, and histopathological diagnosis disclosed high-grade urothelial cancer.[3] In this case, Fukagawa *et al*. supported intraluminal extension via the vas deferens because the patient had a history of HoLEP, which may have opened the ejaculatory duct and allowed malignant cells to penetrate retrogradely and also