Case Report

Recurrent urethral tumor with neuroendocrine differentiation in a female patient after radical cystectomy for bladder cancer

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Abbreviation & Acronyms
BCG = bacillus Calmette-Guérin
CIS = carcinoma *in situ*
MRI = magnetic resonance imaging
non-ONB = nonorthotopic neobladder
ONB = orthotopic neobladder
RC = radical cystectomy
SmCC = small-cell carcinoma
UC = urotherial carcinoma
UR = urethral recurrence

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Introduction: Urethral recurrence after radical cystectomy in female patients with bladder cancer is relatively uncommon. Recurrent bladder tumors with neuroendocrine differentiation are extremely rare.

Case presentation: A 71-year-old female patient who underwent radical cystectomy for bladder cancer presented with vaginal bleeding 19 months postoperatively. She was diagnosed with bladder cancer urethral recurrence. Urethral tumor en-bloc resection with the anterior vaginal wall was performed by combining abdominal and vaginal approaches. Pathological examination revealed a recurrent tumor of urothelial bladder cancer containing small-cell carcinoma components.

Conclusion: This case is the first report of a recurrent tumor with small-cell carcinoma in the female urethra after radical cystectomy for pure urothelial carcinoma.

Key words: bladder cancer, cystectomy, female, small-cell carcinoma, urethral tumor.

Keynote message

Urethral preservation during radical cystectomy for bladder cancer has been considered a safe and reliable option in female patients without urethral or urethral dissection-level tumors. However, our case highlights the possibility of developing a rare pathological type of recurrent urethral tumor if the CIS is located at the bladder neck.

Introduction

UR in females with bladder cancer is an unusual event, even when the urethra is preserved for ONB creation during RC.[1] Moreover, recurrent bladder tumors with neuroendocrine differentiation are extremely rare with only five cases reported since 2000.[2–6] Herein, we describe the first case of simultaneous occurrence of both rare conditions; a recurrent urethral tumor showing neuroendocrine differentiation in a female patient after RC for conventional UC.

Case presentation

A 71-year-old female patient was referred to our department for further atypical cell evaluation in her urine, leading to a pT1 high-grade UC diagnosis associated with CIS at the trigone of the bladder. Subsequent bladder biopsy revealed BCG refractory CIS although the patient was treated with transurethral resection of tumors, followed by an adequate course of intravesical instillation of BCG. She underwent RC with ileal conduit construction because of the high risk of developing invasive high-grade cancer. Intraoperatively, the entire urethrectomy was not performed due to troublesome bleeding from the vascular plexus of the vaginal wall. Cancer cell infiltration was not observed at the urethral margin although the surgical specimen showed scattered CIS involving a large area of the bladder mucosa, including a bladder neck.

The patient began to notice vaginal bleeding 19 months after the RC. MRI was performed 4 months after the onset of the symptom, demonstrating a 25-mm-sized tumor at the blind end of her urethra (Fig. 1). The examination with urethral washing cytology showed malignant cells, and the urethral endoscopy revealed a papillary mass covered with a blood clot. Following the diagnosis of UR of bladder cancer, we performed urethral tumor en-bloc resection with the anterior vaginal wall by combining abdominal and vaginal approaches.

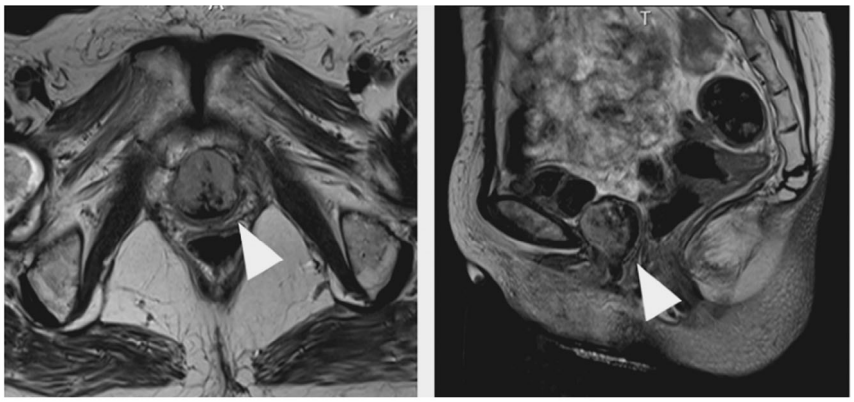

Fig. 1 Pelvic MRI-T2-weighted images (axial; left panel, sagittal; right panel). A 25-mm well-circumscribed round tumor (white arrowhead) is shown at the blind end of the urethra.

Pathological examination demonstrated UC and small round neoplastic cells invading the periurethral muscle. Immunohistochemistry revealed these small round cells as positive for the neuroendocrine markers synaptophysin and CD56 but negative for chromogranin A (Fig. 2). A recurrent tumor with SmCC at the female urethra was diagnosed based on these findings. We reevaluated previous tumor specimens from both transurethral resection and RC but revealed no evidence of neuroendocrine differentiation in either sample. The patient is relapse-free at 6 months of follow-up.

Discussion

RC, including removal of the bladder, distal ureters, uterus, anterior vaginal wall, and urethra, is the standard surgery for females with muscle-invasive bladder cancer.[7] Before the early 1990s, an entire urethrectomy was considered the standard procedure because the female remnant urethra was supposed to be at risk of tumor recurrence after RC.[8] However, the increasing ONB application had questioned the risk of urethral tumor involvement and UR in a female receiving RC.[9] The recent EAU guidelines[7] do not recommend the entire urethral removal in all patients, and ONB is supposed as a safe and reliable option in female patients without urethral or urethral dissection-level tumors. Permanent pathological examination upon RC in our patient revealed CIS lesions and not a tumor near the bladder neck. The tumor recurred at her remnant, blind-ending urethra, presenting with symptomatic bleeding, although the urethral margin had been negative. Histologic examination of the resected urethral tumor demonstrated a quite rare type of recurrent urinary tumor, containing elements of urothelial cell and SmCC.

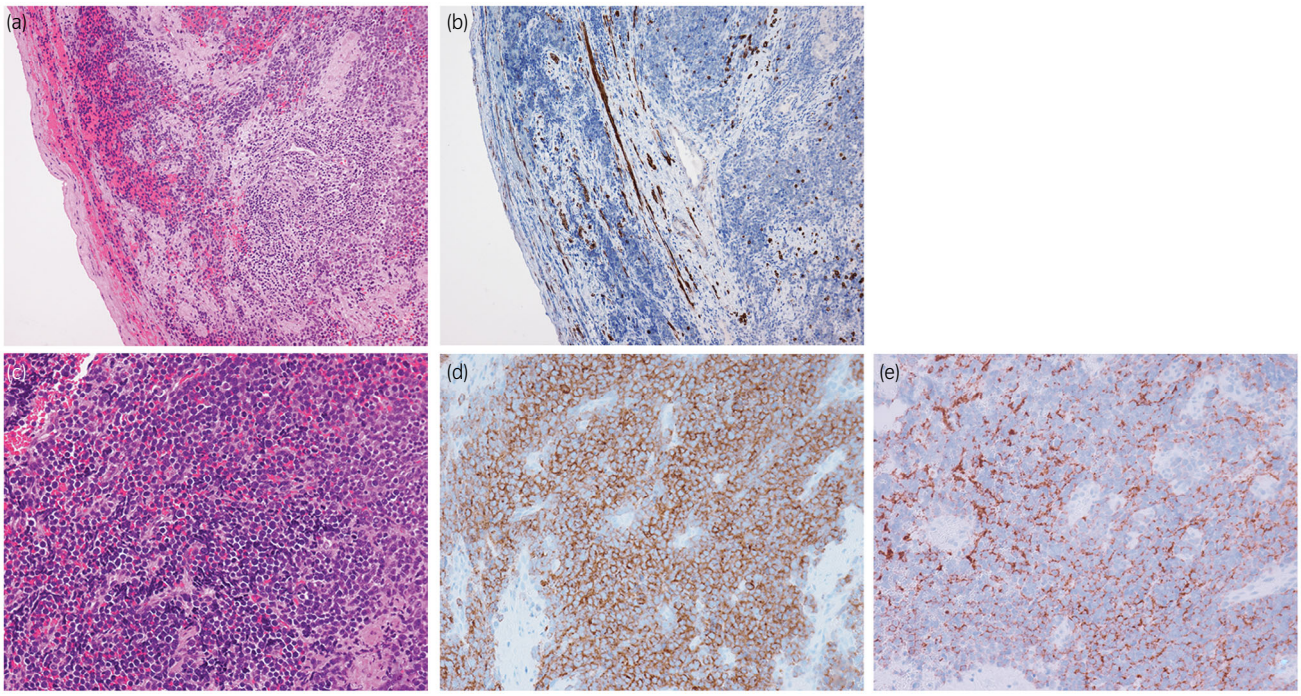

Fig. 2 Microscopic findings. Low-magnification view (×100) shows tumor cells invading the periurethral muscle (a; H&E, b; desmin). A higher power view (×200) reveals diffuse infiltration of neoplastic small round cells (c; H&E). Immunostaining demonstrates that neoplastic cells are positive for synaptophysin (d) and CD56 (e).

Table 1 Urethral recurrence rates in females after non-orthotopic neobladder construction reported in the literature

Reference	Number of female patients (Urethral reccurence patients/total female sample size)	Type of diversion (orthotopic neobladder/ non-orthotopic neobladder)	Urethral reccurence patients (orthotopic neobladder/non-orthotopic neobladder)	Urethral reccurence rate in non-orthotopic neobladder patients
Hassan et al., 2004	1/83	29/54	0/1	1/54 (1.9%)
Clark et al., 2004	0/211	44/167	0/0	0/167 (0%)
Akkad et al., 2006	2/85	46/39	2/0	0/39 (0%)
Boorjian et al., 2011	7/276	16%/84%†	Not reported	7/231.8 (3.0%)‡
Perlis et al., 2013	3/105	29%/71%†	Not reported	3/74.6 (4.0%)¶

†Percentage of each type of diversion in total (male+female) patients. ‡Percentage calculated assuming that 84% of female patients receive non-orthotopic neobladder, and all the urethral recurrence is observed in non-orthotopic neobladder group. ¶Percentage similarly calculated assuming that 71% of female patients receive non-orthotopic neobladder.

SmCC is one of the histologic subtypes of neuroendocrine tumors of the genitourinary tract, in which the bladder is the most common site.[10] It is more common in male than female patients, with a ratio of 3.3:1.0.[10] Most reported cases are mixed variants containing elements, such as UC, squamous cell carcinoma, and adenocarcinoma, as shown in our patient.[5] Both a recurrent bladder tumor containing SmCC and a primary SmCC of the urethra is extremely rare in female patients. Only one case of each has been previously described.[3,11] To our best knowledge, our case is the first report of a recurrent tumor with SmCC in the female urethra after RC for pure UC.

Our case highlights several clinical questions that are simple but difficult to answer. First, safely omit prophylactic urethrectomy in female patients even in non-ONB diversion. Generally, male patients with non-ONB diversion are associated with a higher probability of UR than ONB. Conversely, blind-ending UR of female patients receiving non-ONB diversion has not been fully analyzed because of the limited number of studies[12–16] (Table 1). However, UR has at most a 4% prevalence in those patients; thus, prophylactic urethrectomy could be avoided in most females with non-ONB.

Second, bladder neck CIS cases on the final pathology specimen should consider secondary urethral resection or urethral follow-up in females. A recently proposed algorithm regarding UR follow-up and management after RC[17] recommended that patients with a high-risk factor (e.g., prostatic urethral involvement, bladder neck involvement, CIS) should receive either staged urethrectomy or urethral follow-up, based on the final pathological margin status. Follow-up examinations include clinical symptom screening or urethral wash cytology with or without urethroscopy. However, this algorithm should be carefully adapted to female patients, because it is constructed based on the studies, most of which are mainly focused on male UR. To date, we have not found any definite evidence for the risk of UR in female patients with CIS, especially those in non-ONB. However, we should reflect on the 4-month delay in UR diagnosis after initial urethral bleeding symptoms. Early treatment is warranted to improve the survival of patients with UR because of a definite survival advantage in asymptomatic versus symptomatic diagnoses in patients with UR.[7]

Third, the efficacy of adjuvant chemotherapy in patients with urethral SmCC. Cases with prolonged survival are reported in primary male urethral SmCC with metastasis via cisplatin-based adjuvant chemotherapy.[11] Adjuvant therapy could be justified for a limited disease[10]; however, our patient did not want the treatment with uncertain effects.

Lastly, the type of mechanism involved in developing this rare pathological type of recurrent tumor. The origin of SmCC cells in the urinary bladder has several hypotheses. The most plausible one is that SmCC is differentiated from multipotential cells, including cancer stem cells. This hypothesis is favored because SmCC of the urinary bladder often coexists with other histological components, such as UC, squamous cell carcinoma, or adenocarcinoma.[5] Additionally, both UC and SmCC were observed in tumor tissues in our case, supporting the theory of a common clonal origin even in urethral SmCC.

Conclusion

We have experienced a very rare case of bladder cancer with UC recurrence, including neuroendocrine differentiation in the residual female urethra after RC.

Approval of the research protocol by institutional IRB

Not applicable.

Registry and the registration No. of the study/trial

Not applicable.

Author contributions

Yasuaki Murata: Writing – original draft. Toshiaki Shinojima: Conceptualization; writing – review and editing. Yoko Nakahira: Writing – review and editing. Mei Hamada: Writing – review and editing. Atsushi Sasaki: Supervision; writing – review and editing. Hirotaka Asakura: Supervision.

Conflict of interest

The authors declare no conflict of interest.

Informed consent

Written informed consent was obtained.

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