

Case Report

Urothelial carcinoma occurring in a defunctionalized bladder after urinary diversion due to the bladder exstrophy-epispadias complex

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Abbreviations & Acronyms

BEEC = bladder exstrophy-epispadias complex
CEA = carcinoembryonic antigen
CT = computed tomography
GC = gemcitabine and cisplatin
UC = urothelial carcinoma
UPIII = uroplakin III

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Introduction: The bladder exstrophy-epispadias complex is a rare congenital disease. Urothelial carcinomas rarely occur in patients with this disease, and there have been few reports on its treatment.

Case presentation: We report the case of a 44-year-old man with a hemorrhage from the external urethral meatus. He was diagnosed with bladder exstrophy-epispadias complex and underwent urinary diversion with substitution cystoplasty and Mitrofanoff appendicovesicostomy. Because computed tomography and magnetic resonance imaging suggested invasive bladder carcinoma in the defunctionalized bladder, we performed a cystectomy. The patient was diagnosed with urothelial carcinoma with glandular differentiation. One month after the surgery, nivolumab adjuvant chemotherapy was administered. The patient showed no signs of recurrence or metastasis after the treatment.

Conclusion: This is the first case of adjuvant nivolumab therapy for urothelial carcinoma with the bladder exstrophy-epispadias complex.

Key words: bladder exstrophy, carcinoma, transitional, chemotherapy, adjuvant, epispadias, nivolumab, urinary diversion.

Keynote message

Our article reports a rare case of urothelial carcinoma occurring in a defunctionalized bladder after urinary diversion due to the bladder exstrophy-epispadias complex. This is the first case to show that adjuvant nivolumab was effective for urothelial carcinoma with the bladder exstrophy-epispadias complex.

Introduction

The BEEC is a rare congenital urological disease. With advances in medical technology, the long-term survival of patients with congenital urological diseases is now possible. Herein, we report a case of bladder cancer in a 44-year-old man with a history of BEEC and urinary diversion.

Case report

A 44-year-old Japanese man presented with hemorrhage from the external urethral meatus. The patient was diagnosed with BEEC immediately after birth. Although the patient underwent bladder and abdominal wall closure and urethroplasty at age 6 months, he had an intractable urethral fistula that was not cured even after several operations. Thus, an indwelling urethral catheter was placed to address the incontinence. He had frequent bladder stones and urinary tract infections. Therefore, he underwent urinary diversion with substitution cystoplasty and Mitrofanoff appendicovesicostomy at age 18 years. The original bladder remained defunctionalized, and the patient experienced no problems till age 44 years.

He was a past-smoker, having smoked for 10 years since 20 years. The Eastern Cooperative Oncology Group performance status score was 0. Blood examination showed a high CEA level of 98.1 ng/mL, but the other markers were within normal limits, including prostate-specific antigen. CT revealed thickening of the original bladder wall (Fig. 1a) and swelling of the left internal iliac lymph node (Fig. 1b). Magnetic resonance imaging showed the bladder tumor might have spread into the prostate (Fig. 1c). Since cystourethroscopy and transurethral biopsy were not possible because of the urethral stricture, urinary cytology was infeasible, but a transrectal ultrasound-guided transperineal needle biopsy was performed. The pathological findings revealed high-grade UC. Enhanced CT revealed no other metastases, and the patient was diagnosed with high-grade UC (cT3 or higher, N1, M0). Neoadjuvant chemotherapy with four cycles of

gemcitabine (1000 mg/m²) and cisplatin (70 mg/m²) (GC) over 3 weeks was performed, and the lymph node was reduced. Thus, an open radical cystectomy was performed. A lower abdominal midline incision was used, and the retroperitoneal approach was utilized to reach the defunctionalized bladder. Severe adhesion was observed throughout the Retzius space; therefore, lymph node dissection and urethrectomy could not be performed. Urinary substitution remained intact. The operative time was 10 h and 51 min, with blood loss of 3200 mL. The gross pathology showed that it was impossible to differentiate the bladder, ureter, and prostate (Fig. 2A). Histopathology showed that the carcinoma cells were severely atypical and grew as sheets (Fig. 2B,C) with a gland-like structure (Fig. 2D), suggesting UC with glandular differentiation. Immunohistochemistry revealed a gland-like structure expressing CEA (Fig. 2E). The diagnosis was UC



Fig. 1 CT image showing (a) thickening of the bladder wall (arrowhead) and (b) left internal iliac lymphadenopathy (arrow). (c) Magnetic resonance image showing that the bladder tumor might have spread into the prostate (arrowhead).

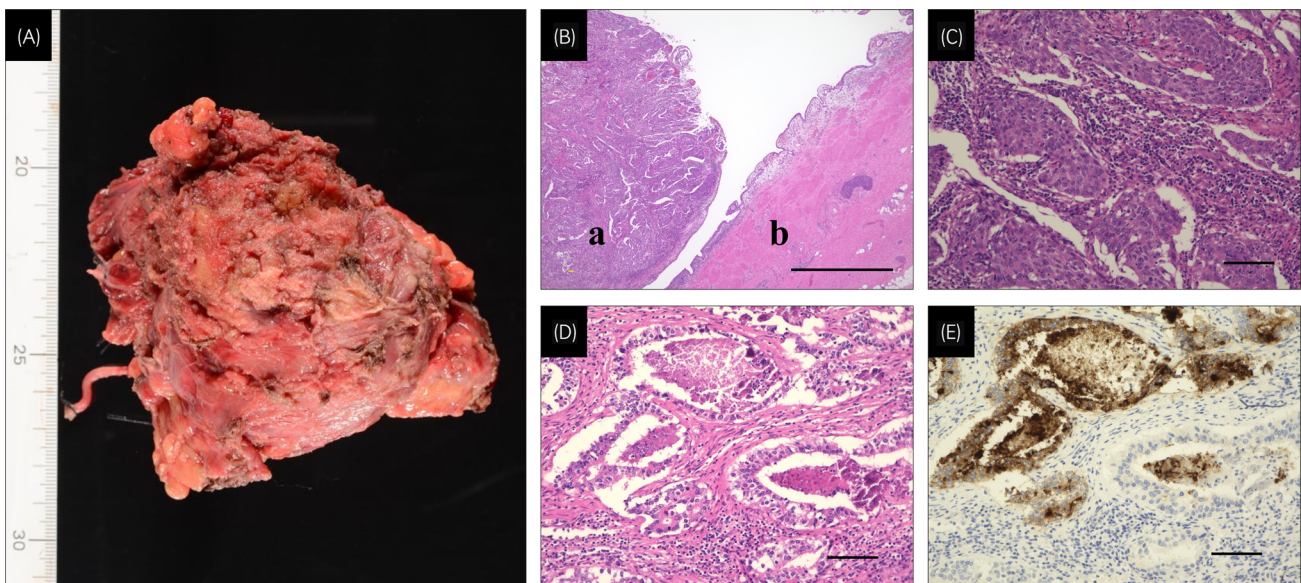


Fig. 2 (A) Gross pathology: A single mass comprising the bladder, prostate, and ureter. The right side is the distal portion. Histopathology: (B) Hematoxylin and eosin staining of (a) urothelial carcinomatous and (b) noncarcinomatous area. (C) Urothelial carcinomatous area in the high-power field, infiltrating plasma cells. (D) Hematoxylin and eosin and (E) immunohistochemical staining for CEA of glandular differentiation (bar = B: 100 μ m, C–E: 2 mm).

with glandular differentiation (high grade, ypT4a). One month after the surgery, weekly adjuvant chemotherapy with nivolumab (240 mg/body weight) was administered. The patient has been recurrence-free for more than 5 months.

Discussion

The incidence of BEEC is 2.15 per 100 000 live births in the United States, and its male-to-female ratio has been reported as 2.3:1.¹ The purpose of surgery is to close the bladder and urethra, reconstruct the external genitalia, and maintain continence, voiding, and sexual function.² The initial closure is ideally performed within the first 48–72 h of life. However, with less bladder capacity, these operations are sometimes performed at 6–12 weeks of age.³ There are two surgical strategies. One is a one-stage reconstruction, including bladder closure, abdominal wall formation, and urethroplasty, and the other is a two-stage reconstruction in which urethroplasty is performed later. Reports indicate that there are no differences in the outcome of continence between these strategies.^{4,5} Unfortunately, our patient required an indwelling urethral catheter because of frequent bladder stones and urinary tract infections.

BEEC is associated with a 694 times higher risk of bladder malignancy.⁶ Many reports indicate that patients with BEEC require lifelong management for complications.^{7–10} Previous reports recommend that patients who receive surgery for UC-associated BEEC should undergo annual cystoscopy^{11,12} and CT.¹² Although no reports recommend ultrasound, it is noninvasive, easy to perform, and might be very useful. A study noted that the median age of patients with UC in the defunctionalized bladder after surgery for BEEC was 39 years, with a report of its occurrence at age 48 years.⁶ Accordingly, we propose annual ultrasound, cystoscopy, and CT until at least age 50 years.

The urothelium comprises umbrella, intermediate, and basal cells on its luminal side. In normal tissues, UPIII is expressed in umbrella cells, and p63 is expressed in intermediate and basal cells. In the case of BEEC, UPIII is absent in 76% of umbrella cells in the bladder epithelium,¹³ suggesting that the epithelium of BCCE lacks umbrella cells. The mechanisms of BEEC carcinogenesis seem to involve chronic irritation, inflammation, and the abnormal nature of the exposed bladder epithelium. In this case, the epithelium of the noncarcinomatous area (Fig. 3a) was negative for UPIII (Fig. 3b) and positive for p63 (Fig. 3c), indicating the absence of umbrella cells. Additionally, the epithelium showed significant plasma cell infiltration, suggesting chronic inflammation, with Masson trichrome staining revealing severe fibrosis in the subcutaneous tissue (Fig. 3d). Therefore, in this case, the lack of umbrella cells associated with disruption of the bladder immune environment and the presence of chronic inflammation may have induced bladder carcinogenesis.

Ninety-five percent of carcinomas in bladder exstrophy are adenocarcinomas, and UCs are rare.⁶ We searched the PubMed database using two keywords “bladder exstrophy” and “urothelial carcinoma” and found four case reports of UC in bladder exstrophy.^{14–17} Three of these four reports involved T4 cases with poor prognoses and no response to chemotherapy with GC. In this case, tumor programmed death ligand 1 staining showed a high tumor proportion score (20%) (Fig. 4), suggesting that postoperative adjuvant therapy with nivolumab for UC may be effective.¹⁸ We plan to treat the current patient with nivolumab for 1 year. To the best of our knowledge, this is the first report of nivolumab administration in a patient with BEEC-associated UC.

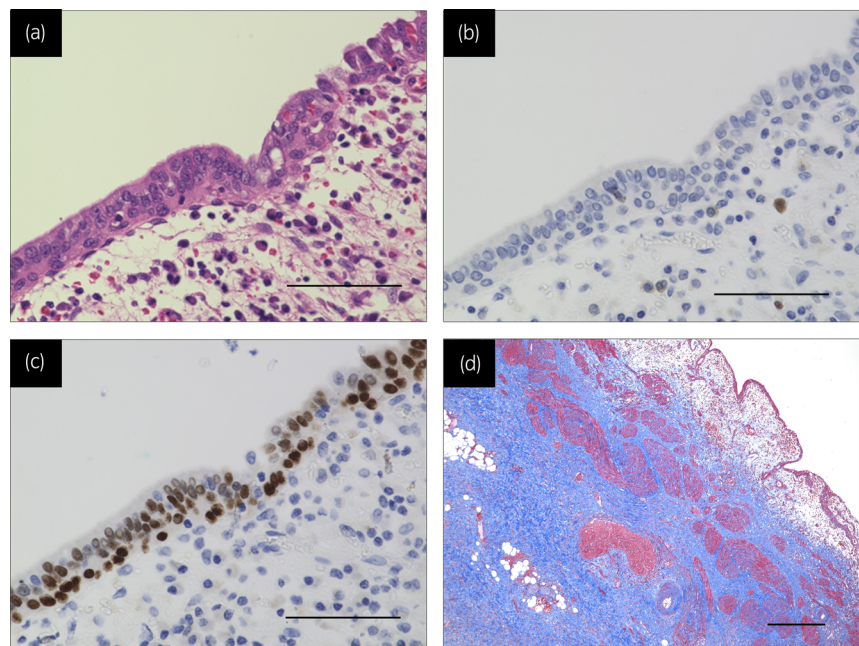


Fig. 3 (a) Hematoxylin and eosin staining. Immunohistochemical staining for (b) Uroplakin-III and (c) p63. (d) Special staining for Masson trichrome for the noncarcinomatous area (bar = a–c: 100 μ m, d: 2 mm).

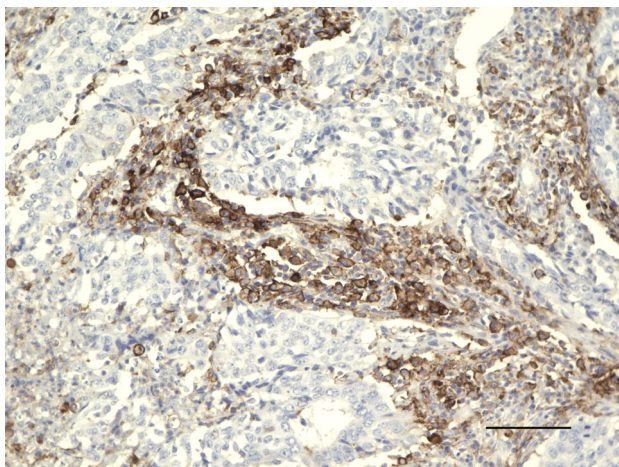


Fig. 4 Immunohistochemical staining for tumor programmed death ligand 1 for the urothelial carcinomatous area (bar = 100 μ m).

Conclusion

We reported a case of adjuvant nivolumab therapy for UC occurring in a defunctionalized bladder after urinary diversion due to BEEC.

Author contributions

Toshiharu Morikawa: Investigation; methodology; project administration; writing – original draft. Shoichiro Iwatsuki: Supervision; validation; writing – review and editing. Aya Naiki-Ito: Supervision; writing – review and editing. Masakazu Gonda: Supervision; writing – review and editing. Kazumi Taguchi: Supervision; writing – review and editing. Taku Naiki: Supervision; writing – review and editing. Shuzo Hamamoto: Supervision; writing – review and editing. Atsushi Okada: Supervision; writing – review and editing. Takahiro Yasui: Supervision; writing – review and 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 was approved by the Institutional Review Board of Nagoya City University Hospital (IRB approved number: 60-23-0017) and conformed to the provisions of the Declaration of Helsinki.

Informed consent

Informed consent was obtained from the patient.

Registry and the Registration No. of the study/trial

Not applicable.

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