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Complete remission following pembrolizumab therapy for a patient with nephroureterectomy positive-margin carcinoma in situ and bladder cancer unresponsive to Bacille Calmette–Guérin therapy

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Abstract

An 82-year-old man was diagnosed with synchronous non-muscle-invasive bladder cancer and left lower ureteral carcinoma. He underwent transurethral resection of the bladder tumor, followed by total left nephroureterectomy after preoperative chemotherapy with four courses of gemcitabine and carboplatin. Histopathological findings showed positive-margin carcinoma in situ. In addition, since recurrence of non-muscle-invasive bladder cancer was observed in the bladder, Bacille Calmette–Guérin intravesical infusion therapy was performed, but the cancer persisted due to treatment resistance. After that, pembrolizumab therapy was performed, and complete remission was achieved.

Keywords

Bladder cancer, ureteral cancer, Bacille Calmette–Guérin intravesical infusion therapy-unresponsive, pembrolizumab therapy

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Introduction

The incidence of synchronous non-muscle-invasive bladder cancer (NMIBC) and upper urothelial carcinoma was reported to be found 1.8% in patients with primary NMIBC who underwent initial examination of the upper urinary tract.[1] We encountered a patient with synchronous NMIBC and left lower ureteral cancer. Systematic treatment has yet to be established for synchronous NMIBC and upper urothelial carcinoma.

Case report

An 82-year-old man was emergently brought to our hospital with fever and left abdominal pain in April 2020 and was hospitalized with a diagnosis of bilateral acute pyelonephritis. Computed tomography (CT) at the time of admission showed a left lower ureteral tumor (Figure 1(a)). Urine cytology at admission was positive for cancer cells. Cystoscopy revealed multiple papillary tumors around the right ureteral orifice. Magnetic resonance imaging showed multiple tumors from the posterior wall to right wall of the bladder and the muscle-invasive tumor in the lower part of the left ureter (Figure 1(b) and (c)). He received TUR-BT (Transurethral Resection of Bladder Tumor) in May 2020. Pathological findings were urothelial carcinoma, high

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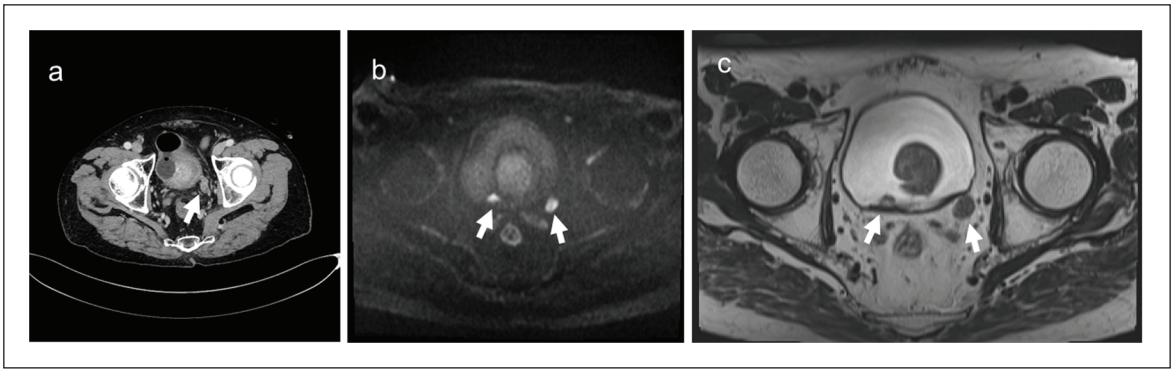

Figure 1. Computed tomography (CT) at the time of admission shows a left lower ureteral tumor (a: arrow). A high signal intensity on diffusion-weighted imaging (b: arrow) and a low signal intensity on T2-weighted imaging (c: arrow) of magnetic resonance imaging show multiple non-muscle-invasive tumors from the posterior to right wall of the bladder and the muscle-invasive tumor in the lower part of the left ureter.

grade, G2 > G3, and pT1 (Figure 2(a)). Carcinoma in situ was not detected in this TUR specimen. One week after the operation, he was urgently admitted with oliguria and acute renal failure. Bilateral hydronephroses were mild on CT, and hemodialysis was performed temporarily. There were few renal and prerenal factors as possible causes of renal failure. Therefore, postrenal factors were considered, and right nephrostomy was performed. After the right nephrostomy, diuresis occurred, and he recovered from renal failure. He received four preoperative courses of gemcitabine and carboplatin chemotherapy for left lower ureteral muscle-invasive cancer. The lower ureteral cancer shrank slightly on CT, and the urinary cytology became negative, so left radical nephroureterectomy was performed in November 2020. Pathological findings of the ureteral tumor following neoadjuvant chemotherapy showed invasive urothelial carcinoma, high grade, G2 > G3, ypT2, and positive-margin carcinoma in situ at bladder cuff (Figure 2(b)). After that, the intravesical washing cytology was positive for cancer cells, and cystoscopy showed flat velvet-like mucosa and no obvious tumor, so biopsy was performed in November 2020. Histopathological findings showed non-invasive urothelial carcinoma, high grade, G2. From January 2021, the patient was treated with Tokyo 172 strain Bacille Calmette–Guérin (BCG) 80 mg intravesical infusion therapy once a week for a total of eight times, according to the results of clinical trials in Japan.[2] The temporary intravesical washing cytology was negative, but cystoscopy showed the persistence of bladder cancer in June 2021. We presented the patient with the treatment options of recurrent tumors following BCG therapy including BCG intravesical therapy rechallenge, radical cystectomy, or pembrolizumab therapy. He hoped pembrolizumab therapy. He has been receiving pembrolizumab therapy since July 2021 (200 mg once every 3 weeks, 400 mg once every 6 weeks from December 2021). Biopsy of bladder tumor in August 2021 following four cycles of pembrolizumab was performed and the histopathological findings showed urothelial carcinoma, high grade, G2 (Figure 2(c)). Following eight cycles of pembrolizumab, the intravesical washing cytology became negative, and cystoscopy showed no residual tumor. Transurethral resection of the obstruction site of the right ureteral orifice was performed in January 2022 and a right ureteral catheter was inserted. The resected specimen was scarred tissue and confirmed negative for tumor. The right nephrostomy catheter was removed. He underwent transurethral resection of the prostate for obstructive benign prostatic hypertrophy in April 2022. He has been receiving pembrolizumab therapy (400 mg once at 6-week intervals), and no recurrence had been observed as of April 2023.

Discussion

Although there is a low incidence of synchronous upper urothelial carcinoma and NMIBC, the upper urothelial carcinoma lesions are invasive in a high proportion of cases.[1] Patients with a tumor in the trigone have a sixfold higher risk of a synchronous tumor in the upper urinary tract. The present patient had multiple papillary tumors around the right ureteral orifice.

Latest studies examining the role of neoadjuvant and adjuvant chemotherapy for upper tract urothelial cancer show that perioperative chemotherapy was beneficial for prolonging survival; however, the evidence for adjuvant chemotherapy was stronger than that for neoadjuvant chemotherapy.[3] However, a recent literature suggested that the benefit of neoadjuvant chemotherapy in upper tract urothelial carcinoma is similar to that found in urothelial carcinoma of the bladder.[4]

The most known schedule of BCG intravesical therapy consists of six weekly instillations, followed by maintenance with three weekly instillations at months 3, 6, 12, 18, 24, and 30 in international guidelines; however, in Japan, most patients with existing papillary bladder cancer or carcinoma in situ of the bladder are treated with Tokyo 172 strain BCG

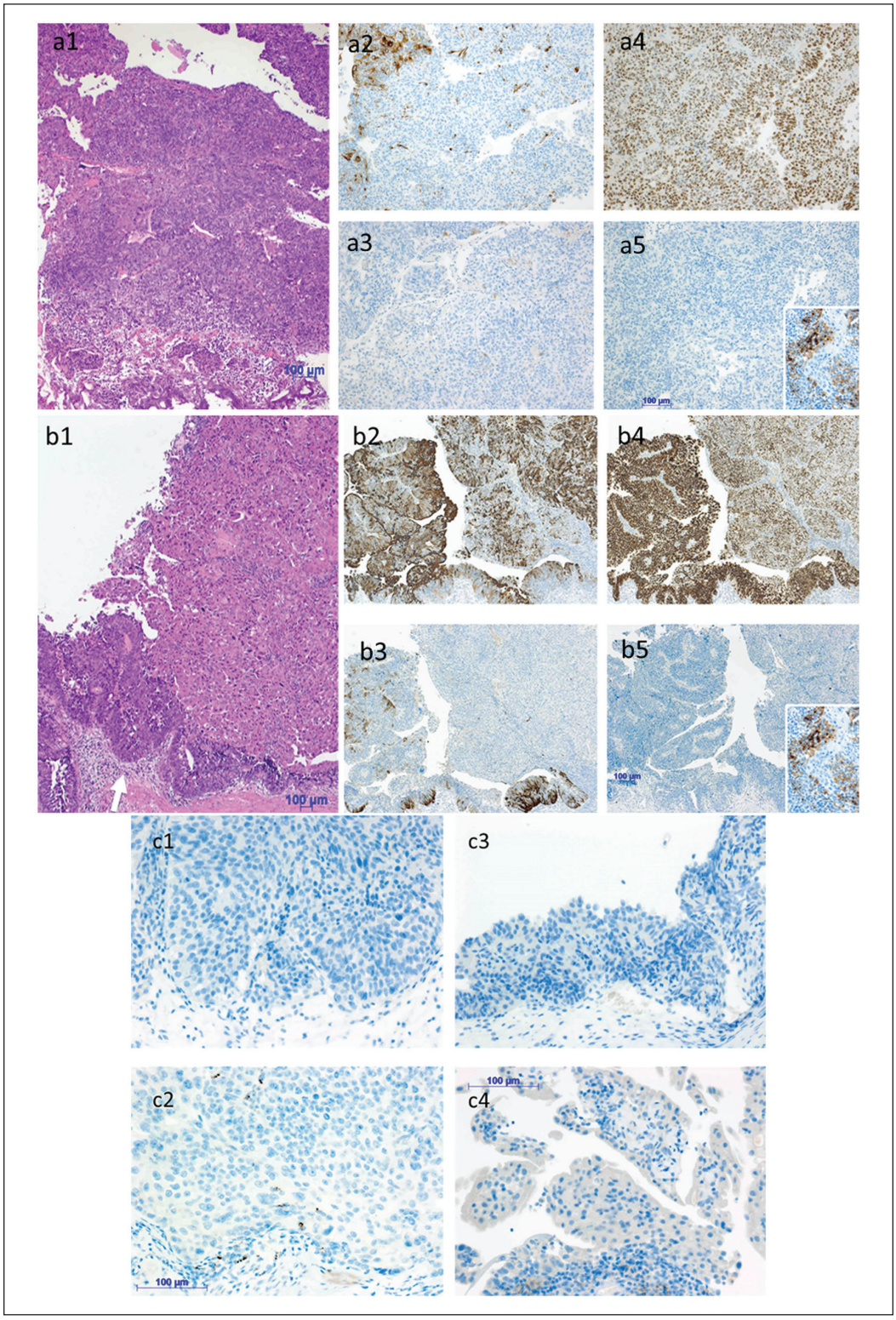

Figure 2. Pathological findings. (a) Pathological findings of bladder carcinoma show urothelial carcinoma, high grade, G2 > G3, pT1 (a1: hematoxylin–eosin staining), CK20 weakly positive (a2), CK5/6 negative (a3), GATA3 positive (a4), and PD-L1 negative (a5) (insert; positive control). (b) Pathological findings of left lower ureteral carcinoma show invasive ureteral carcinoma, high grade, G2 > G3, pT2 (b1: hematoxylin–eosin staining, arrow: positive-margin carcinoma in situ), CK20 positive (b2), CK5/6 weakly positive (b3), GATA3 positive (b4), and PD-L1 negative (b5) (insert; positive control). (c) The cancer tissues during the treatment courses in the present patient did not express PD-L1 (c1: TUR-BT in May 2020, c2: ureteral cancer in November 2020, c3: bladder tumor biopsy in November 2020 before BCG intravesical infusion therapy, c4: bladder tumor biopsy in August 2021 following four cycles of pembrolizumab).

intravesical instillation; 80 mg weekly for eight times, according to the results of clinical trials in Japan.[2,5,6]

Systematic treatment has yet to be established for synchronous NMIBC and upper urothelial carcinoma; however, TUR-BT is performed for both diagnosis and treatment as was the case for the present patient.[5] After that, we treated the patient with neoadjuvant chemotherapy using gemcitabine and carboplatin. Pathological findings of the ureteral tumor following neoadjuvant chemotherapy showed invasive urothelial carcinoma, high grade, G2 > G3, ypT2, and positive-margin carcinoma in situ at bladder cuff. In the guidelines, adjuvant nivolumab in patients with ypT2 and/or ypN+ disease after neoadjuvant chemotherapy and nephroureterectomy is offered based on the results of CheckMate 274 trial; however, in Japan, pembrolizumab was reported to improve the prognosis of patients with early relapsing disease after the receipt of platinum-based perioperative chemotherapy for highly malignant tumors of the upper urinary tract.[7–9]

Among intravesical infusion therapy agents, BCG is the only agent associated with a decreased progression risk versus TUR-BT alone.[10] However, despite high initial response rates, up to 50% of patients develop recurrence or become BCG-unresponsive. Recently, pembrolizumab monotherapy was reported to show promising antitumor activity in patients with BCG-unresponsive NMIBC.[11]

The present patient was treated with BCG intravesical infusion therapy but showed persistence of bladder cancer. He has been receiving pembrolizumab therapy. Complete remission was achieved, and no recurrence has been observed. Immune checkpoint molecules, such as PD-1 (programmed cell death protein 1)/PD-L1 (Programmed cell Death 1- Ligand 1), have been reported to be closely associated with the suppression of antitumor immunity, and their inhibitors have been used to treat various cancers including bladder cancer. Hashizume et al.[12] demonstrated that expression of PD-L1 was enhanced on tumor tissue after BCG treatment in BCG-resistant NMIBC patients. The cancer tissues during the treatment courses in the present patient did not express PD-L1; however, complete remission was achieved with pembrolizumab therapy (Figure 2(c)). Using the expression of PD-L1, it can be difficult to estimate the response to pembrolizumab therapy in patients with BCG-unresponsive NMIBC. The development of biomarkers for estimating responsiveness of immunotherapies will be needed in the future.

Genome-wide analyses revealed basal and luminal subtypes of urothelial carcinomas.[13] Immunohistochemical subtyping has been reported to be able to identify basal and luminal subtypes of urothelial carcinomas.[14,15] In the present patient, the immunohistochemical subtypes were different between the bladder cancer tissue and ureteral cancer tissue (Figure 2(a) and (b)). These differences are unclear, and a clonal difference may exist between the bladder cancer tissue and ureteral cancer tissue. Recently, it was reported that molecular biological properties of upper urothelial carcinoma may differ from those of bladder carcinoma.[16] Molecular biological properties will hopefully be applied to treatment in the future.

Conclusion

We encountered a patient who showed complete remission following pembrolizumab therapy for nephroureterectomy positive-margin carcinoma in situ and bladder cancer unresponsive to BCG therapy. New therapies such as pembrolizumab therapy will be expected to become the standard of care for patients with bladder cancer unresponsive to BCG therapy.

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Author's contributions

TN is the corresponding author, wrote of original draft, and reviewed. RN wrote of original draft and reviewed. GH interpreted pathological findings and reviewed. YI and NH reviewed. All authors reviewed and edited the manuscript and approved the final version.

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Ethics approval

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Informed consent

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