

CASE REPORT

Nagoya J. Med. Sci. **84**. 865–870, 2022
doi:10.18999/nagjms.84.4.865

A case of undifferentiated carcinoma of the bladder treated by combination therapy of surgery, local radiation, and immune checkpoint inhibitors

Wataru Nakane, Yushi Naito, Koya Morishita, Kazuna Matsuo,
Shohei Ishida and Yoshihisa Matsukawa

Department of Urology, Nagoya University Graduate School of Medicine, Nagoya, Japan

ABSTRACT

Undifferentiated carcinoma of the bladder is a rare malignancy with a poor prognosis. We present the case of an 81-year-old woman complaining of bladder irritation. Computed tomography (CT) and magnetic resonance imaging (MRI) revealed a bulky bladder tumor, which was diagnosed as cT4aN0M0. A trans-urethral resection of the bladder tumor revealed pT2 or higher urothelial carcinoma. The patient underwent total cystectomy with an ileal conduit diversion. Histological examination revealed a primary undifferentiated bladder carcinoma with a sarcoma component, pT3aN0M0. Postoperative adjuvant chemotherapy with gemcitabine plus carboplatin was administered. However, this regimen was discontinued after one course due to significant myelosuppression. Four months after total cystectomy, a pelvic tumor with suspected local recurrence was detected on CT. The patient was diagnosed with recurrent undifferentiated carcinoma with a sarcoma component by a transperineal ultrasound-guided biopsy. Local radiation therapy and immunotherapy with immune checkpoint inhibitors were prescribed. After three courses of immunotherapy with pembrolizumab, the primary tumor disappeared. Upon continuing immune checkpoint inhibitor treatment, the patient has maintained a complete response without tumor recurrence in the following six months.

Keywords: undifferentiated carcinoma, bladder, immune checkpoint inhibitors, radiation therapy, abscopal effect

Abbreviations:

CT: computed tomography

ICI: immune checkpoint inhibitor

MRI: magnetic resonance imaging

TILs: tumor-infiltrating lymphocytes

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Received: October 7, 2021; accepted: December 8, 2021

Corresponding Author: Wataru Nakane, MD

Department of Urology, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan

Tel: +81-52-744-2985, Fax: +81-52-744-2319, E-mail: wataru.nakane@med.nagoya-u.ac.jp

INTRODUCTION

Undifferentiated carcinoma of the bladder is defined as an undifferentiated epithelial malignancy that cannot be classified under any histological category. It was included among the “poorly differentiated carcinomas” by the recent World Health Organization classification.¹ It is reportedly rare, occurring in 0.6–0.9% of bladder cancer cases, and it has a poor prognosis.² While the treatment strategy has not been established, various combinations of surgery, radiotherapy, and chemotherapy have been proposed. However, most cases were refractory to treatment.² We report the successful treatment of undifferentiated bladder carcinoma with a multidisciplinary approach, involving surgery, immune checkpoint inhibitor (ICI), and radiation.

CASE REPORT

An 81-year-old Japanese woman consulted a local doctor for bladder irritation. Her past medical history includes significant hypertension and hyperlipidemia. She underwent iliac artery stenting for internal iliac artery aneurysm, simple hysterectomy for fibroid tumors, and total hip arthroplasty for a fracture of the left femoral neck. There was no family history of bladder or renal disease. Ultrasonography revealed right hydronephrosis and an extensive bladder tumor, and the patient was referred to our hospital. Upon admission, the patient’s physical examination findings were unremarkable. Her serum creatinine level was elevated at 3.88 mg/dL due to right ureteral obstruction. The values of the tumor markers, such as carcinoembryonic antigen, cancer antigen 19-9, and squamous cell carcinoma, were within the normal ranges, and the urine cytology test results were negative. A non-papillary broad-based tumor in the triangular area was observed on cystoscopy. Computed tomography (CT) and magnetic resonance imaging (MRI) revealed right hydronephrosis and a bulky bladder tumor, which was suspected to have infiltrated the vagina. However, no distant metastasis was observed. Based on these findings, she was diagnosed with a bladder tumor, cT4aN0M0, stage IIIA (Fig. 1a, 1b).³ A transurethral resection of the bladder tumor was performed. The pathological diagnosis was G3, pT2, or more invasive uroepithelial carcinoma. Shortly after that, a total cystectomy was performed without preoperative chemotherapy. Due to her previous history of iliac artery stenting surgery, lymph

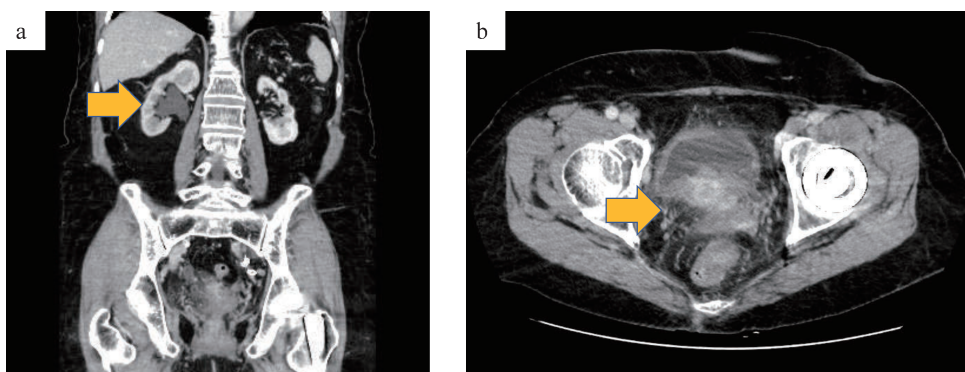


Fig. 1 The initial diagnosis by contrast-enhanced computed tomography (CT) scan was cT4aN0M0, stage IIIA

Fig. 1a: Coronal section of the CT scan showing right hydronephrosis.

Fig. 1b: Axial section of the CT scan suggesting vaginal invasion.

node dissection was not performed. Pathological examination revealed an undifferentiated bladder carcinoma with some sarcoma components and multiple tumor-infiltrating lymphocytes (TILs) (Fig. 2a). In the immunostaining study, the tumor was negative for GATA3 staining, which shows positive for urothelial components, and positive for AE1/AE3 staining, which is useful for differentiating undifferentiated cancer from non-epithelial malignancies. The tumor infiltrated the surrounding lipid tissue and was diagnosed as pT3aN0M0, stage IIIA. Postoperative adjuvant chemotherapy with gemcitabine plus carboplatin was administered because the risk of recurrence was high. However, chemotherapy was discontinued after one course due to febrile neutropenia and grade 4 thrombocytopenia. As shown in Fig. 3a, a pelvic mass was detected on follow-up CT four months after the total cystectomy. The lesion was diagnosed as a recurrence by transvaginal needle biopsy. The histopathology of this biopsy documented a greater sarcoma component than that of the histopathology from the total cystectomy (Fig. 2b). Local resection was considered impractical because of the early postoperative recurrence and patient's pathological findings. In addition, because the bladder tumor obtained by total cystectomy (Fig. 2c) and transvaginal needle biopsy (Fig. 2d) showed diffusely positive by programmed cell death ligand 1 (PD-L1) staining (E1L3N[®]), she underwent radiation therapy, immediately followed by ICI treatment with pembrolizumab. After three courses of ICI treatment, the recurrent tumor disappeared (Fig. 3b). The patient continued undergoing ICI treatment, and no recurrence was observed in the following six months (Fig. 4).

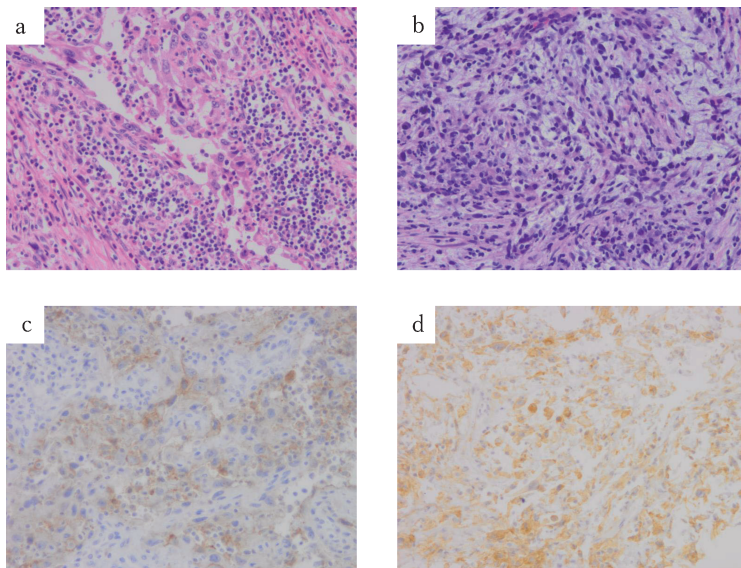


Fig. 2 Hematoxylin and eosin (HE) staining and PD-L1 (programmed cell death ligand 1) staining of specimens obtained by total cystectomy and transvaginal needle biopsy

Fig. 2a: HE staining of bladder tumor obtained by total cystectomy.

Undifferentiated carcinoma, containing some sarcoma components and numerous tumor-infiltrating lymphocytes, is identified.

Fig. 2b: HE staining of specimens obtained by transvaginal needle biopsy.

The sarcoma component is increased, compared with the total cystectomy findings.

Fig. 2c: PD-L1 staining (E1L3N[®]) of bladder tumor obtained by total cystectomy.

High PD-L1 expression is observed in tumor cells.

Fig. 2d: PD-L1 staining (E1L3N[®]) of specimens obtained by transvaginal needle biopsy.

High PD-L1 expression is observed in tumor cells, while surrounding lymphocytes are negative for PD-L1 staining.

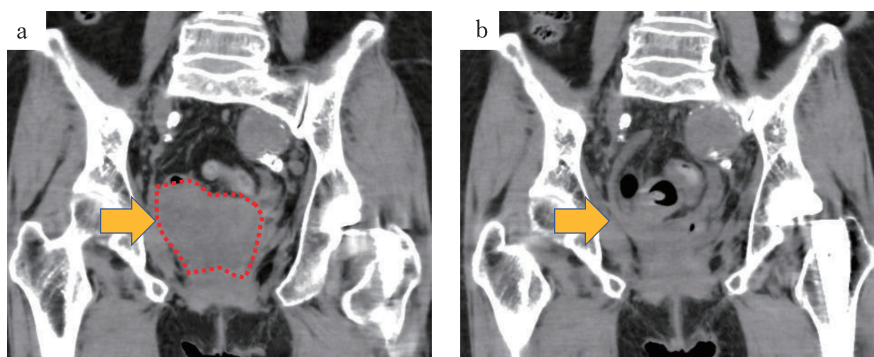


Fig. 3 CT scan before and after pembrolizumab administration

Fig. 3a: Four months after total cystectomy, a recurrent lesion occupying the pelvis is detected.

Fig. 3b: A complete response was achieved after three courses of pembrolizumab.

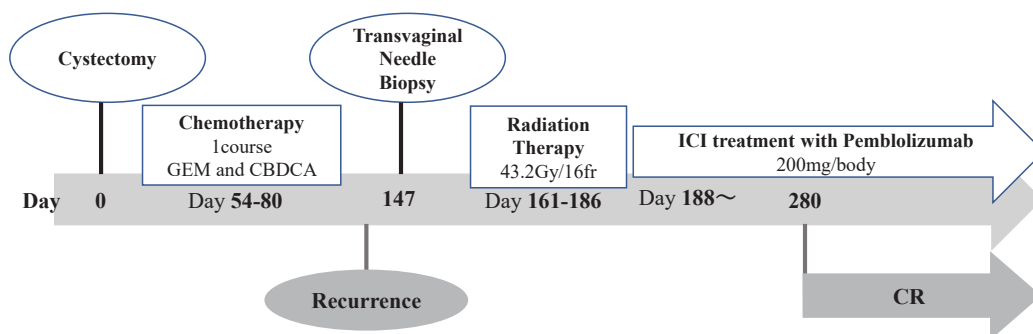


Fig. 4 Clinical course of the combination therapy

GEM: gemcitabine
 CBDCA: carboplatin
 CR: complete response

DISCUSSION

Undifferentiated bladder cancer is often refractory to various treatments. Moreover, these tumors rarely regress completely after multidisciplinary treatment, as observed in this case. The mechanisms underlying the complete response, achieved by multidisciplinary treatment in this case, remain incompletely understood. However, a hypothesis, based on three aspects, including ICI, radiation therapy, and surgical treatment, was discussed in this study.

First, the cancer tissue in this case had a 1) high expression rate of TILs, 2) high expression rate of PD-L1, and 3) sarcoma-like components. It is suggested that these tissue and immunological features of this tumor may be involved in its significant response to ICI treatment. Recent studies have reported that ICI treatment was effective against muscle-invasive bladder cancer. In the ABACUS trial,⁴ the efficacy of atezolizumab, a PD-L1 antibody, was evaluated prospectively in patients with cT2-T4a muscle-invasive bladder cancer and the therapeutic effects of ICI, including life expectancy and achievement rate of complete response, was reported to be significantly high in patients with an increase in CD8-positive T lymphocytes in cancer tissue. Since CD8-positive T lymphocytes are considered surrogate markers for TILs, ICI treatment was more effective in

patients with a high expression rate of TILs in cancer tissue. In the KEYNOTE-045 study,⁵ which evaluated the efficacy of pembrolizumab as second-line therapy for urothelial carcinoma in patients with disease progression after platinum-based chemotherapy, the overall survival was significantly better among patients with a high expression of PD-L1 on histopathology. In this case, as shown in Fig. 2c and 2d, the PD-L1 expression in both the primary bladder tumor and recurrent tumor in the pelvis was high based on posterior immunostaining. Additionally, the pathological findings of the recurrent tumor were predominantly sarcoma-like components. This possibly enhanced the effect of pembrolizumab, which was reportedly effective in reducing the tumor size in patients with undifferentiated sarcomas, according to the SARC028 study.⁶

Second, the immediate initiation of ICI treatment after radiation therapy likely contributed to the complete response. Undifferentiated carcinoma is highly radiosensitive.^{7,8} Basic studies have documented the synergistic effect between ICI therapy and radiation therapy.⁹ In clinical practice, the abscopal effect¹⁰ of radiotherapy reportedly enhanced the antitumor effect of ICI treatment. The PACIFIC study¹¹ evaluated the efficacy of durvalumab after chemoradiation against unresectable locally advanced non-small-cell lung cancer. Based on this study, ICI treatment administered immediately after radiation therapy significantly improved progression-free survival.

Third, the absence of lymph node dissection during total cystectomy due to stenting of the internal iliac artery aneurysm possibly contributed to the successful treatment of recurrent tumors. Lymph node dissection reportedly suppressed the priming phase function in the cancer-immune cycle. In a basic study that compared the therapeutic effects of PD-L1 antibodies with and without lymph node dissection in mice with carcinoma, tumor size reduction and survival were significantly better in the group without lymph node dissection.¹² In this case, the absence of lymph node dissection possibly enhanced antitumor immunity during the radiation and ICI treatment for recurrent tumors.

In conclusion, we reported a case of undifferentiated bladder cancer that was completely cured by multidisciplinary treatment combining radiotherapy, ICI therapy, and surgical treatment. Although further follow-up is needed in the future, this treatment protocol suggested a new treatment strategy for undifferentiated bladder cancer.

ACKNOWLEDGEMENTS

We would like to thank Editage (www.editage.com) for English language editing.

CONFLICT OF INTEREST STATEMENT

The authors state that they have no conflict of interest.

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