Case Report

Successful treatment with enfortumab–vedotin of metastatic signet ring cell cancer expressing nectin-4 and originating from the bladder

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Abbreviations & Acronyms
5-FU = fluorouracil
AE = adverse event
AraC = cytarabine
CDDP = cisplatin
CEA = carcinoembryonic antigen
CT = computed tomography
DOD = death from this disease
DTX = docetaxel
EPI = epirubicin
EV = enfortumab–vedotin
GC = gemcitabine+cisplatin
GN = gemcitabine+nedaplatin
MMAE = monomethyl auristatin E
MMC = mitomycin C
MRI = magnetic resonance imaging
mSRCUU = metastatic signet ring cell carcinoma of the urinary bladder
MTX = methotrexate
OK-432 = streptococcus
Pem = pembrolizumab
SRCUU = signet ring cell carcinoma of the urinary bladder
UFT = tegafur/uracil

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Introduction: As an aggressive adenocarcinoma phenotype, primary signet ring cell carcinoma of the urinary bladder is an extremely rare variant. The prognosis of metastatic signet ring cell carcinoma of the urinary bladder is extremely poor and the clinical course for its specific pathogenesis remains unelucidated.
Case presentation: A 64-year-old Japanese male patient was diagnosed with invasive urothelial carcinoma with glandular differentiation of a signet ring cell–type with pT4aN0M0, and he was eventually diagnosed with metastatic signet ring cell carcinoma of the urinary bladder. He was initially responsive to systemic combination induction chemotherapy of S-1 and cisplatin followed by avelumab switch maintenance therapy; however, signet ring cell carcinoma of the urinary bladder relapse occurred in the pathological findings of a biopsy from the right thigh. Immunohistochemical analysis of this specimen identified strong positive staining for nectin-4 and, following enfortumab–vedotin treatment, the patient showed a good response.
Conclusion: We thus describe a rare case of metastatic signet ring cell carcinoma of the urinary bladder with nectin-4 expression diagnosed by a biopsy of a metastatic site.

Key words: enfortumab–vedotin, image-guided biopsy, lymphatic metastasis, nectins, signet ring cell carcinoma of the urinary bladder.

Keynote message

The use of EV as a result of immunohistochemical analysis of nectin-4 in the early stage would likely be a promising treatment for mSRCCU.

Introduction

An aggressive adenocarcinoma phenotype, SRCCU is an extremely rare variant, accounting for 0.24% of all bladder malignancies.[1] Patient survival is usually poor since SRCUU presents at an advanced stage. In Japan, at 2 years, overall and cancer-specific survival rates were 43% and 45%, respectively. Notably, patients with stage IV disease at diagnosis were not alive after 2 years.[2] Above all, the clinical data on mSRCCU is inadequate and the choice of treatment is very limited.[3,4]

Case presentation

A Japanese male, aged 64 years, presented with pain during urination lasting for 1 month. Abdominal CT showed a uniformly enhanced thickened right wall of the bladder but no suspected metastatic lesions (Fig. 1a,b). MRI revealed diffuse low intensity on T2-weighted images and uniform high intensity with focal strong intensity on diffusion-weighted images. These findings suggested advanced T-stage bladder cancer (Fig. 1c,d). Various serum tumor markers were found to be within normal range including serum CEA levels (3.6 ng/mL).

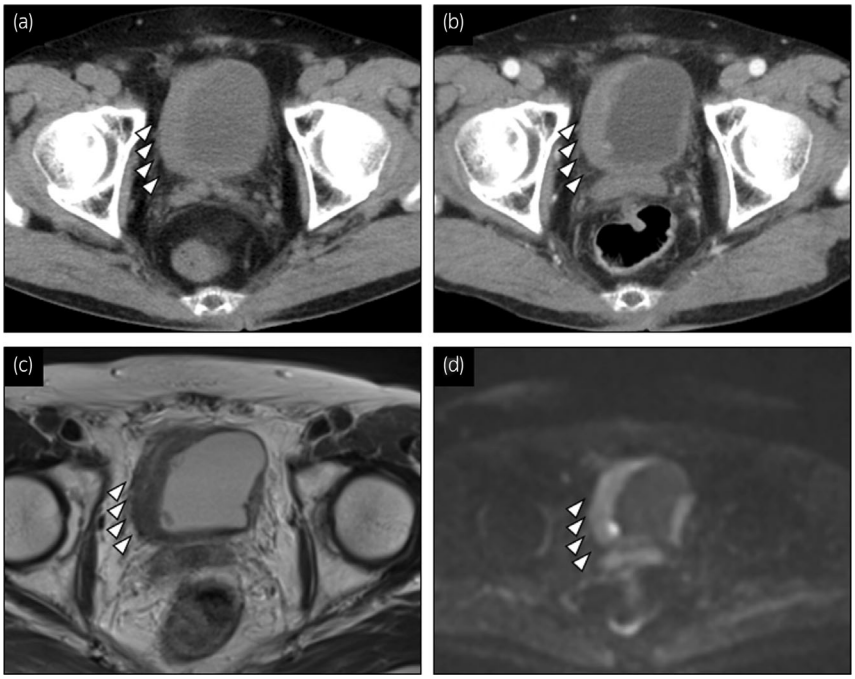

Fig. 1 Abdominal CT showed a uniformly enhanced thickened right wall of the bladder with no suspected metastatic lesions (plain: a, enhanced: b). MRI revealed diffuse low intensity on T2-weighted images and uniform high intensity with focal strong intensity on diffusion-weighted images; these suggested advanced-T stage bladder cancer (T2: c, diffusion: d). (white arrowheads).

After informed consent, a transurethral resection of the papillary lesion was performed; histopathological findings diagnosed a high-grade urothelial carcinoma (Fig. 2a). Therefore, laparoscopic radical cystectomy with urinary diversion was performed. Macroscopic pathological findings revealed a wide range of erosive protruded lesions with a post-resection scar but no papillary tumor remnants. Microscopically, urothelial carcinoma was observed in a small portion of the epithelium (Fig. 2b,c). Atypical cells with tubular formation were partially observed but most were occupied by infiltrating signet ring cells in a solitary manner (Fig. 2b,d–f). Signet ring cells invaded into the surrounding fatty tissue and seminal vesicles (pT4a). These results indicated invasive urothelial carcinoma with glandular differentiation of a signet ring cell–type with pT4aN0M0. Nineteen months after the radical surgery, serum CEA became elevated to 7.4 ng/mL (normal range: 0.1–5.0 ng/mL), and CT revealed a circumferential wall thickness with edema from the sigmoid colon to the rectum. Pathological findings in specimen obtained by colon fiber revealed atypical cells, therefore, the patient was diagnosed with mSRCCU. After informed consent, induction chemotherapy of a combination regimen of S-1 and CDDP was performed. After 7 cycles, diagnosed as a partial response, a switch maintenance therapy with avelumab was undertaken. However, the sudden emergence of right leg edema emerged and CT revealed an irregular thickness of subdermal and muscle tissues in the right thigh (Fig. 2g). A biopsy specimen of the percutaneous route revealed signet ring cells in the adipose tissue around the skeletal muscle (Fig. 2h). The serum CEA became elevated to 18 ng/mL and, therefore, third-line EV treatment was administered. After 3 cycles of treatment, the ascites disappeared, and both symptoms and CT images of the right thigh improved (Fig. 2i) in addition to a decline of the serum CEA level to 8.6 ng/mL. Though AEs occurred, including grade 1 taste disturbance, a grade 1 localized rash, and grade 1 blurry vision, these were controllable. In total, the patient underwent 9 cycles of successful treatment of third-line EV. However, the patient developed pleural effusion, finally, he died of cancer after palliative therapy 29 months after the initiation of induction treatment for mSRCCU.

Discussion

In Table 1, all previous studies with regard to the regimen of induction chemotherapy for patients with mSRCCU in Japan are summarized. Of note is that the use of platinum-based therapy may be associated with an improvement in prognosis. In addition, we previously reported the efficacy of a combination regimen of S-1 and CDDP in SRCCU and metastatic adenocarcinoma originating from the bladder; therefore, in this case, this regimen was selected. Above all, S-1 is the most widely used 5-fluorouracil–based drug for gastric cancer, including signet ring cell carcinoma, furthermore, we previously reported on a case of metastatic adenocarcinoma in the bladder that was successfully treated with S-1 and CDDP. This suggests such induction chemotherapy is a powerful tool that can control mSRCCU.[4]

Recently, immune checkpoint inhibitor (ICI) drugs, and novel antibody–drug conjugates, including EV, have changed the sequential treatment landscape. In mSRCCU, only one article described as to the sequential treatment of ICI (avelumab) after CDDP-based chemotherapy, however, after three courses of treatment, rapidly progressed.[13] As an antibody–drug conjugate, EV is a human monoclonal antibody against nectin-4 and MMAE, a microtubule-disrupting agent, leads to cell-cycle arrest and death, and showed significant survival benefit compared to chemotherapy for previously treated locally advanced or metastatic urothelial carcinoma in the EV-301 trial.[14] Nectin-4 was expressed in the urothelial

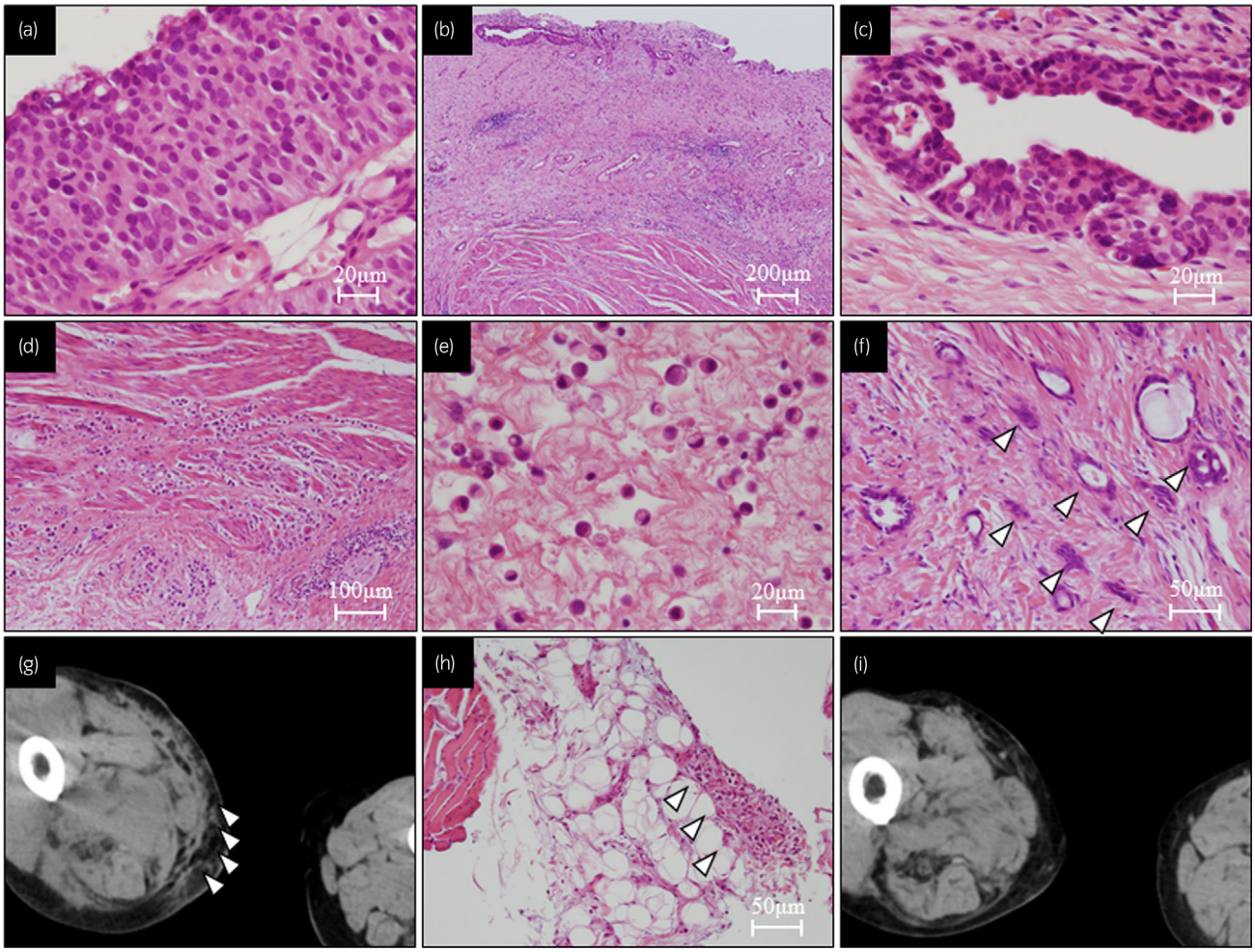

Fig. 2 Transurethral resection of the bladder tumor was performed. Hematoxylin–eosin staining of histopathological findings led to a diagnosis of high-grade urothelial carcinoma (a). Microscopically, urothelial carcinoma was observed in a small portion of the epithelium (low magnification: b, urothelial carcinoma: c), and atypical cells in tubular formation were partially observed (arrowheads) (f), but most of these were occupied by infiltrating signet ring cells (d, e) in a solitary manner. CT revealed irregular thickness of subdermal and muscle tissues in the right thigh (arrowheads) (g). A biopsy specimen using a percutaneous route revealed signet ring cells in the adipose tissue around the skeletal muscle (arrowheads) (h). Third-line treatment was administered. Three cycles of treatment were given, with improvement of both symptoms and CT images of the right thigh (i).

Table 1 Summary of all previous representative cases that received induction chemotherapy for mSRCCU in Japan

Author (published year)	Age (years)	Gender Male: M Female: F	TNM classification	Induction chemotherapy regimen	Follow-up duration (months)	Survival outcome
Kato *et al.*[5] (1987)	74	F	cT4N1M0	MMC + 5FU + AraC	5	Survived
Nagata *et al.*[6] (1991)	50	M	cT4N0M1b	OK-432 + 5FU + UFT	5	DOD
Taue *et al.*[7] (2004)	42	M	cT4N0M0	MTX + CDDP	11	DOD
Nanpo *et al.*[8] (2005)	59	F	cT4N1M1	MTX + 5FU	9	DOD
Mizuma *et al.*[9] (2010)	83	M	cT4bN0M1	S-1	12	Survived
Akamatsu *et al.*[2] (2010)	55	F	cTxN1M0	S-1	5	DOD
Akamatsu *et al.*[2] (2010)	76	M	cTxN1M0	S-1 + Carboplatin	2	DOD
Uchiyama *et al.*[10] (2012)	63	M	cT4bN2M1	GC	18	DOD
Tagami *et al.*[11] (2012)	64	M	cT4bN2M0	S-1 + CDDP	14	Survived
Kitakaze *et al.*[12] (2017)	64	M	cT4bN0M0	S-1 + CDDP	12	Survived
Ishii *et al.*[13] (2023)	55	F	cT3bN2M1	GC	12	DOD
Current case	65	M	pT4aN0M1	S-1 + CDDP	29	DOD

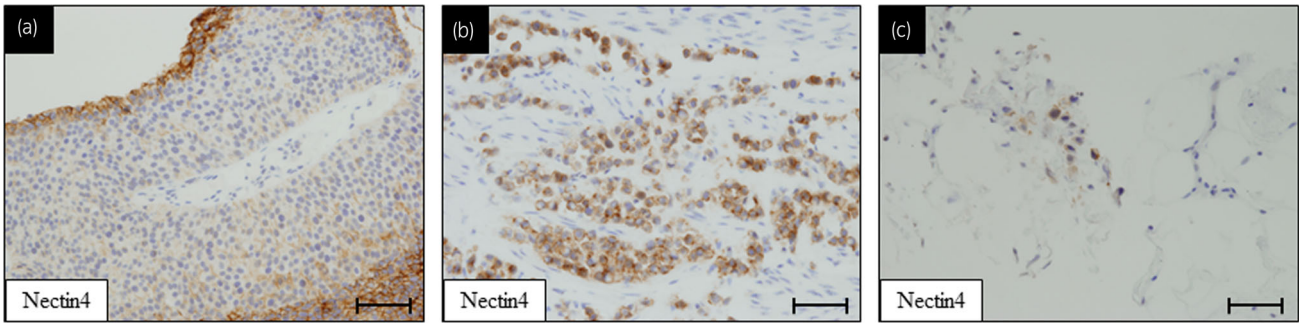

Fig. 3 Nectin-4 expression. Transurethral resection specimen: a, cystectomy specimen: b, specimen obtained by biopsy from a metastatic site: c.

epithelium of the bladder and localized predominantly in the cell membrane or cell membrane and cytoplasm of tumor cells. Patients showing high expression of nectin-4 tended to obtain a better outcome compared with patients with low expression.[15] However, precise data as to the expression level in variant type, including adenocarcinoma, is very limited. In our case, nectin-4 was expressed on the plasma membrane of signet ring cells in the cystectomy specimen (Fig. 3a,b) in almost the same intensity levels. And total of 9 cycles of successful treatment of third-line EV was performed with tolerable AE profiles. Recently, Klümper *et al*.[16] suggested that by a prognostic analysis according to nectin-4 expression both at the original and metastatic sites, nectin-4 expression decreased significantly during metastatic spread. In addition, patients with a low nectin-4 status in a biopsy specimen of a metastatic site tended to show less benefit from EV. The AE profiles from EV treatment were generally worse compared with those of ICI. Therefore, EV should be selected when patients have a good performance status or have satisfied prognostic factors in an early-line setting. In our case, nectin-4 was highly expressed also in the metastatic specimen (Fig. 3c) at the same level compared with the radical specimen. Therefore, even in patients with mSRCCU, for the early switch treatment of EV, the evaluation of biopsy tissue from metastases would be able to predict the efficacy of such treatment. Such a new treatment strategy might lead to developing of personalized treatment approaches by a companion diagnosis.

Conclusion

We describe a rare case of mSRCCU in a patient who survived long term after a sequential strategy of CDDP-based chemotherapy and avelumab switch maintenance, and EV treatment. This entity is a very aggressive phenotype and nectin-4 status might predict the effectiveness of EV.

Author contributions

Maria Aoki: Resources; writing – original draft. Taku Naiki: Conceptualization; writing – review and editing. Aya Naiki-Ito: Formal analysis. Toshiharu Morikawa: Data curation. Nayuka Matsuyama: Data curation. Koei Torii: Data curation. Taiki Kato: Data curation. Tetsuji Maruyama: Data curation. Shingo Inaguma: Data curation. Takahiro Yasui: Supervision.

Conflict of interest

The authors declare no conflict of interest.

Approval of the research protocol by an Institutional Reviewer Board

The ethics committees of Nagoya City University Graduate School of Medical Sciences approved this study and written informed consent was obtained according to the World Medical Association Helsinki Declaration (in 1975) (IRB No. 1638).

Informed consent

The patient gave written informed consent for the publication of this article and accompanying images.

Registry and the Registration No. of the study/trial

Not applicable.

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