Case Report

Relapsed urachal carcinoma responding to first-line chemotherapy with capecitabine-oxaliplatin plus bevacizumab

Akihiko Hatano,[1] Kunihiko Wakaki,[2] Norio Miyajima[1] and Shuichi Komatsu[1]

Departments of [1]Urology and [2]Pathology, Niigata Prefectural Shibata Hospital, Shibata, Niigata, Japan

Abbreviations & Acronyms
CapeOX = capecitabine and oxaliplatin
CDDP = cisplatin
CDX2 = caudal type homeobox transcription factor 2
CEA = carcinoembryonic antigen
CK = cytokeratin
CT = computed tomography
FOLFIRI = leucovorin, 5-fluorouracil, and irinotecan
FOLFOX = leucovorin, 5-fluorouracil, and oxaliplatin
MUC = mucin
NCCN = National Comprehensive Cancer Network
S-1 = tegafur-gimeracil-oteracil potassium
UrC = urachal carcinoma

Correspondence: Akihiko Hatano MD, PhD, Department of Urology, Niigata Prefectural Shibata Hospital, 1-2-8, Honcho, Shibata, Niigata 957-8588, Japan.
Email: ahatano@sbthp.jp

How to cite this article: Hatano A, Wakaki K, Miyajima N *et al*. Relapsed urachal carcinoma responding to first-line chemotherapy with capecitabine-oxaliplatin plus bevacizumab. *IJU Case Rep*. 2023; 6: 345–348.

Received 18 March 2023; accepted 28 July 2023.
Online publication 9 August 2023

Introduction: Advanced urachal carcinoma has a poor prognosis; however, a standard systemic treatment has not been established. We treated a patient with relapsed urachal carcinoma with capecitabine-oxaliplatin plus bevacizumab, a standard regimen for colon cancer, and obtained favorable responses.

Case presentation: A 47-year-old woman presented with hematuria. Under the diagnosis of non-metastatic urachal carcinoma, an extended partial cystectomy was performed. Histopathological examination revealed adenocarcinoma with negative surgical margins and lymph nodes. Thirty-two months postoperatively, lung metastases and local recurrence were confirmed, along with elevated carcinoembryonic antigen levels, and nine chemotherapy cycles were administered. Subsequently, the recurrent lesion regressed, and tumor marker levels normalized. Fourteen months after treatment discontinuation, the disease remained stable without progression.

Conclusion: This is the first report of advanced urachal carcinoma treated with capecitabine-oxaliplatin plus bevacizumab, demonstrating the potential of this treatment as first-line chemotherapy for this disease.

Key words: bevacizumab, capecitabine, chemotherapy, oxaliplatin, urachal carcinoma.

Keynote message

CapeOX plus bevacizumab combination therapy is worth considering as a first-line chemotherapeutic option for advanced UrC.

Introduction

UrC is a rare malignant bladder dome tumor accounting for only 0.2%–0.7% of all bladder cancers.[1,2] Since most of these tumors arise in the submucosa or extravesical layer, they are usually asymptomatic during early disease and are often diagnosed in advanced stages.[1,2] Metastatic or recurrent UrC has an extremely poor prognosis. As a primary treatment approach, partial or radical cystectomy with *en bloc* resection of the urachal ligament with the umbilicus and lymphadenectomy is recommended for localized disease.[3] However, owing to its rarity, standard systemic management for advanced cases remains unestablished.

The most common histological subtype of UrC is mucin-producing adenocarcinoma with enteric features.[1,2,4] Based on the histopathological similarities between colon cancer and UrC, chemotherapeutic regimens for colon cancer have recently been used for advanced UrC, with reported efficacy.[5–10] However, the usefulness of CapeOX plus bevacizumab, one of the standard first-line chemotherapy regimens for advanced colon cancer, is unclear. We report a case of relapsed UrC that responded well to CapeOX plus bevacizumab treatment.

Case presentation

A 47-year-old woman presented to our hospital with intermittent asymptomatic gross hematuria that had persisted for 18 months. Urine cytology at the first visit was negative. Ultrasonography and cystoscopy revealed a 3 cm sessile tumor in the bladder dome (Fig. 1). CT and magnetic resonance imaging revealed a mass at the bladder dome, suggesting extraserosal

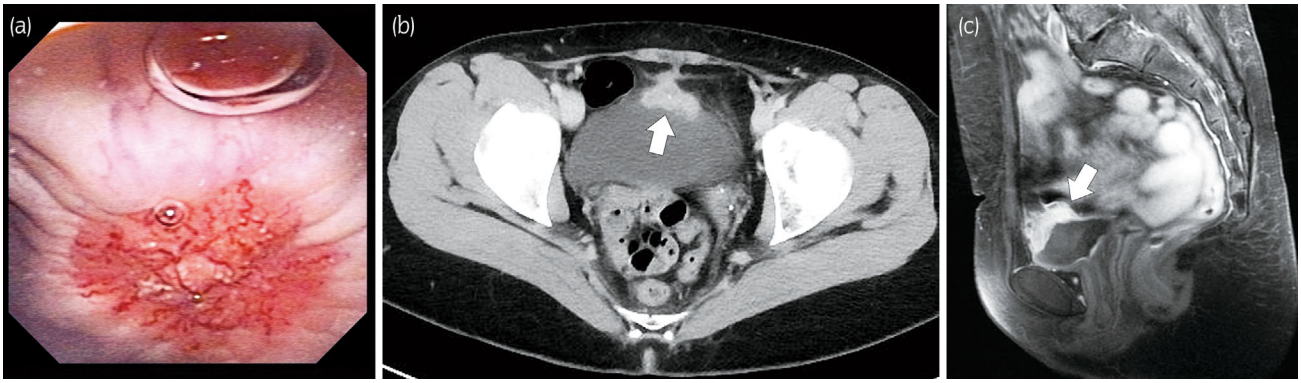

Fig. 1 Cystoscopy revealed a bulging submucosal tumor with central telangiectasia (a). CT scan (b) and post-contrast magnetic resonance imaging (c) showed a mass lesion at the bladder dome extending toward the umbilical ligament (white arrow), suggesting extraserosal invasion.

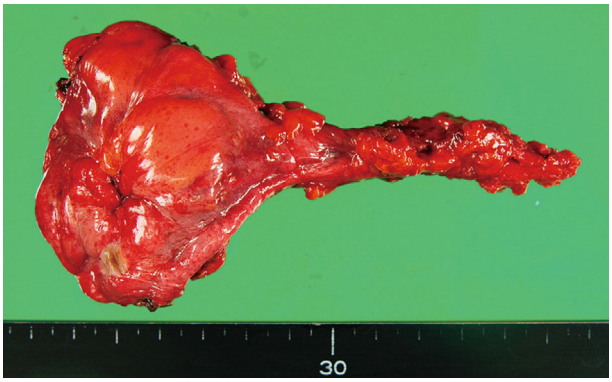

Fig. 2 The peritoneal aspect of the resected specimen. A dimple is observed in the center of the tumor. The tumor size is 20 × 17 × 38 mm.

invasion (Fig. 1). No evidence of metastasis was observed. The serum CEA level was elevated at 15.9 ng/mL (normal <5.0 ng/mL). Histopathological examination of the tissue obtained by transurethral resection of the bladder tumor showed adenocarcinoma with muscle invasion, suggestive of UrC.

The patient was diagnosed with non-metastatic UrC and underwent partial cystectomy with *en bloc* resection of the urachal ligament with the umbilicus, as well as bilateral pelvic lymphadenectomy (Fig. 2). Histopathological examination revealed a well-differentiated enteric-type adenocarcinoma growing through the muscularis propria of the bladder and invading the peritoneal subserosa and the bladder submucosa (Sheldon stage IIIA)[1] (Fig. 3). Immunohistochemical staining was positive for MUC2, CK7, CK20, CDX2, and CEA, but negative for MUC1, MUC5AC, MUC6, and nuclear β-catenin. The pathologic resection margins were negative, and there were no lymph node metastases.

One month postoperatively, the serum CEA level normalized. Thereafter, we followed up with CT scans and CEA measurements every 3 months. Four months postoperatively, the patient's serum CEA level began to increase gradually, but CT identified no recurrent lesions. Thirty-two months postoperatively, her serum CEA level had risen to 12.5 ng/mL, and CT scans confirmed multiple lung metastases and

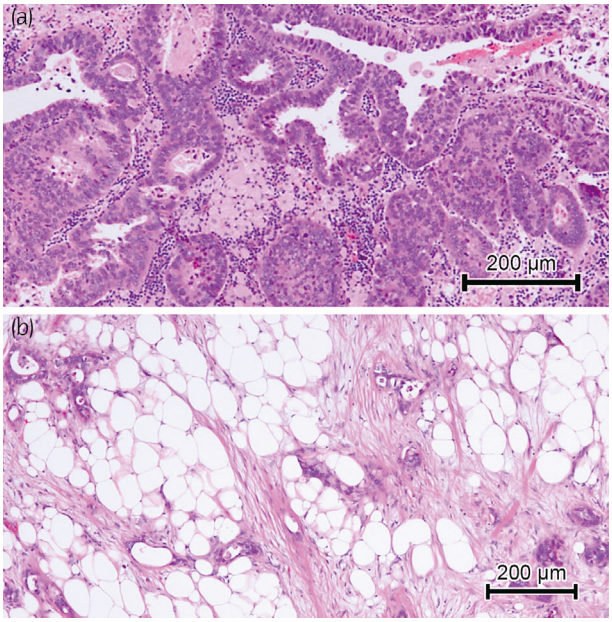

Fig. 3 Histopathological preparation of the primary lesion stained with hematoxylin & eosin. (a) Well-differentiated enteric-type adenocarcinoma. Columnar epithelial cells with cellular and nuclear pleomorphism and loss of epithelial polarity form irregular glandular structures. (b) Cancer cells infiltrating the subserosal fat tissue.

local recurrence on the left side of the bladder (Fig. 4). She had no subjective symptoms.

One month after confirmation of relapse, we initiated CapeOX plus bevacizumab. Laboratory findings, including liver and kidney function, were normal at the start of chemotherapy. CapeOX consisted of a 2-h intravenous infusion of oxaliplatin 130 mg/m^2 on day 1, followed by oral capecitabine 1000 mg/m^2 twice daily for 14 days in a 3-week cycle. Bevacizumab was administered as a 30- to 90-min intravenous infusion before oxaliplatin at a dose of 7.5 mg/kg on day 1.[11] CT scans after three cycles of chemotherapy confirmed size reduction of both the lung metastases and local recurrent lesion. After six cycles, her serum CEA levels normalized. During chemotherapy, anemia (grade 2)[12] and neutropenia (grade 2)[12] were observed as adverse events that

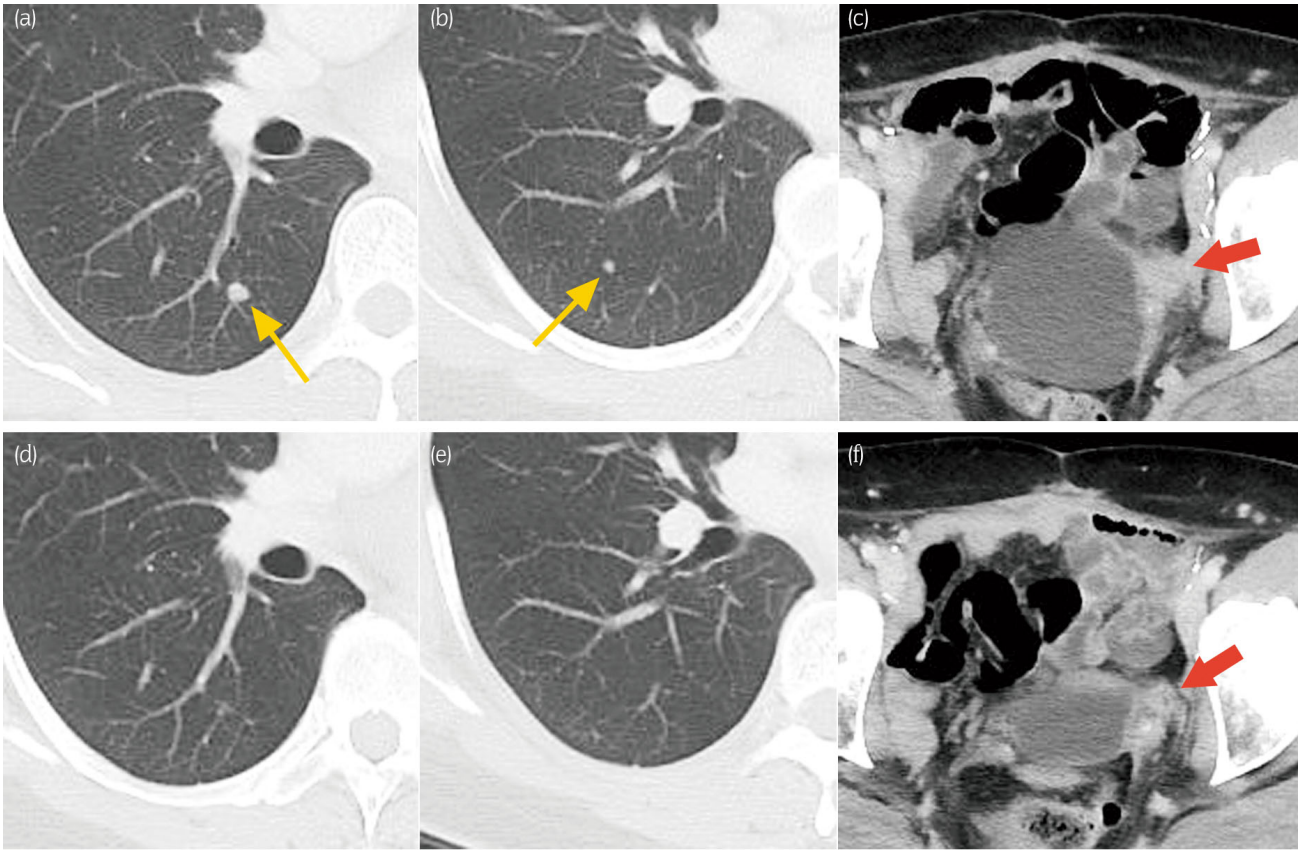

Fig. 4 Upper row: CT scans at recurrence. (a), (b) Two metastases in the lower lobe of the right lung (yellow arrows). (c) Local recurrence on the left side of the bladder (red arrow). Lower row: CT scans 14 months after discontinuing the chemotherapy. (d), (e) The lung metastases had disappeared. (f) The local recurrent lesion remained regressed (red arrow).

could be treated by adjusting the drug dosage and administration interval. Anorexia, nausea, and diarrhea were observed early in treatment. Following nine cycles of chemotherapy, CT scans demonstrated further shrinkage of the recurrent lesions. However, the treatment was interrupted due to unacceptable peripheral sensory neuropathy (grade 3).[12] We offered the patient to continue treatment, excluding oxaliplatin, but she declined. Fourteen months after discontinuing chemotherapy, CT scans showed that the lung metastases had disappeared, and the size of the local recurrence remained reduced (Fig. 4). Her serum CEA level remained within normal limits.

Discussion

Due to its rarity, the appropriate systemic treatment for advanced UrC remains unestablished. However, chemotherapeutic regimens for colon cancer have recently been used to treat UrC based on their pathological similarities. Currently, the cornerstone drugs of first-line regimens for unresectable or metastatic colon cancer include fluoropyrimidines, platinum-based drugs, and irinotecan. The NCCN Guidelines for Colon Cancer list FOLFOX, CapeOX, FOLFIRI, and their combination with bevacizumab as standard primary systemic treatments for patients for whom intensive therapy is recommended.[11] For colon cancer, no significant differences in treatment outcomes have been observed between FOLFOX, FOLFIRI, and CapeOX.[13,14] Bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor, has additive effects when used in combination with these chemotherapy regimens.[15,16]

In advanced UrC, S-1/CDDP therapy was once noted. This regimen also consists of an oral fluoropyrimidine and a platinum agent, and is currently the first-line standard for unresectable gastric cancer in Japan, but is not included as standard therapy in the latest guidelines for advanced colon cancer. Since Kojima *et al*. reported a case of complete remission in 2006,[17] there have been several reports showing some presumptive efficacy, but there have also been reports of ineffective cases,[10] and some currently evaluate its efficacy as modest.[18] Recently, several studies have reported the efficacy of FOLFOX, CapeOX, FOLFIRI,[5–9] and FOLFIRI plus bevacizumab.[10] However, to our knowledge, there have been no reports on the efficacy of CapeOX plus bevacizumab. In our case, the immunohistochemical staining pattern overlapped with that of typical colon cancer, except that CK7 was positive and nuclear β-catenin was negative. Accordingly, we administered CapeOX plus bevacizumab, and the therapeutic effects met our expectations. Regarding adverse events, unacceptable peripheral sensory neuropathy led to the interruption of chemotherapy; however, other adverse effects were tolerable.

Adverse event profiles vary by regimen, with oxaliplatin-containing regimens tending to cause peripheral neuropathy and irinotecan tending to cause alopecia. In CapeOX, hand-

foot syndrome should be considered, and severe diarrhea is rare. When administering fluoropyrimidine, FOLFOX and FOLFIRI require a continuous intravenous infusion of 5-fluorouracil for 46 h at home. In contrast, in CapeOX, capecitabin is administered orally for 14 days. This eliminates the need for implantation of a central venous access port, which is a major benefit for patients. An appropriate regimen should be selected on a case-by-case basis, considering the patient's background and each regimen's characteristics.

Postoperative adjuvant chemotherapy for high-risk, localized UrC is of great interest. However, previous reports have failed to demonstrate its benefit.[19] Second-line chemotherapy for relapse after first-line therapy for advanced UrC also remains unestablished. If our patient relapses again in the future, we would use a regimen containing irinotecan, according to colon cancer guidelines; FOLFILI plus bevacizumab would be the first choice. When a central venous access port is unavailable, combination therapy with oral fluoropyrimidines, such as capecitabine, is an option.[20]

Conclusion

This is the first report of relapsed UrC treated with CapeOX plus bevacizumab, demonstrating the potential of this combination as a first-line chemotherapy option. Further case accumulation is expected to verify the efficacy of this regimen for UrC with different stages of progression, metastatic sites, and grades of malignancy.

Acknowledgments

The authors would like to thank Editage (www.editage.com) for the English language editing.

Author contributions

Akihiko Hatano: Conceptualization; data curation; visualization; writing – original draft. Kunihiko Wakaki: Investigation; visualization; writing – review and editing. Norio Miyajima: Writing – review and editing. Shuichi Komatsu: 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 off-label use of chemotherapeutic agents in this study was approved by the Ethics Committee of Niigata Prefectural Shibata Hospital (Approval No. 2021-22).

Informed consent

Written informed consent was obtained from the patient.

Registry and the Registration No. of the study/trial

Not applicable.

References

1 Sheldon CA, Clayman RV, Gonzalez R, Williams RD, Fraley EE. Malignant urachal lesions. *J. Urol.* 1984; **131**: 1–8.
2 Mylonas KS, O'Malley P, Ziogas IA, El-Kabab L, Nasioudis D. Malignant urachal neoplasms: a population-based study and systematic review of literature. *Urol. Oncol.* 2017; **35**: 33.e11–33.e19.
3 NCCN Clinical practice guidelines in oncology (NCCN guidelines). Bladder Cancer. Version 2.2022.
4 Gopalan A, Sharp DS, Fine SW *et al*. Urachal carcinoma: a clinicopathologic analysis of 24 cases with outcome correlation. *Am. J. Surg. Pathol.* 2009; **33**: 659–68.
5 Tran B, McKendrick J. Metastatic urachal cancer responding to FOLFOX chemotherapy. *Can. J. Urol.* 2010; **17**: 5120–3.
6 Yanagihara Y, Tanji N, Miura N *et al*. Modified FOLFOX6 chemotherapy in patients with metastatic urachal cancer. *Chemotherapy* 2013; **59**: 402–6.
7 Siefker-Radtke A. Urachal adenocarcinoma: a clinician's guide for treatment. *Semin. Oncol.* 2012; **39**: 619–24.
8 Yasui M, Jikuya R, Tatenuma T *et al*. Urachal carcinoma with peritoneal dissemination treated with chemotherapy and surgical resection leading to prolonged survival with no recurrence. *Case Rep. Urol.* 2018; **2018**: 9836154.
9 Chen M, Xue C, Huang RQ *et al*. Treatment outcome of different chemotherapy in patients with relapsed or metastatic malignant urachal tumor. *Front. Oncol.* 2021; **11**: 739134.
10 Kanamaru T, Iguchi T, Yukimatsu N *et al*. A case of metastatic urachal carcinoma treated with FOLFIRI (irinotecan and 5-fluorouracil/leucovorin) plus bevacizumab. *Urol. Case Rep.* 2015; **3**: 9–11.
11 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Colon Cancer. Version 2.2022.
12 U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Published: November 27, 2017.
13 Tournigand C, André T, Achille E *et al*. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J. Clin. Oncol.* 2004; **22**: 229–37.
14 Cassidy J, Clarke S, Díaz-Rubio E *et al*. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. *J. Clin. Oncol.* 2008; **26**: 2006–12.
15 Saltz LB, Clarke S, Díaz-Rubio E *et al*. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J. Clin. Oncol.* 2008; **26**: 2013–9.
16 Yamazaki K, Nagase M, Tamagawa H *et al*. Randomized phase III study of bevacizumab plus FOLFIRI and bevacizumab plus mFOLFOX6 as first-line treatment for patients with metastatic colorectal cancer (WJOG4407G). *Ann. Oncol.* 2016; **27**: 1539–46.
17 Kojima Y, Yamada Y, Kamisawa H, Sasaki S, Hayashi Y, Kohri K. Complete response of a recurrent advanced urachal carcinoma treated by S-1/cisplatin combination chemotherapy. *Int. J. Urol.* 2006; **13**: 1123–5.
18 Urasaki T, Naito Y, Matsubara N, Sasaki M, Kogawa T, Hosono A. Cisplatin and S-1 for urachal carcinoma: a single-institution case series. *IJU Case Rep.* 2019; **2**: 150–4.
19 Guerin M, Miran C, Colomba E *et al*. Urachal carcinoma: a large retrospective multicentric study from the French Genito-urinary tumor group. *Front. Oncol.* 2023; **13**: 1110003.
20 Xu RH, Muro K, Morita S *et al*. Modified XELIRI (capecitabine plus irinotecan) versus FOLFIRI (leucovorin, fluorouracil, and irinotecan), both either with or without bevacizumab, as second-line therapy for metastatic colorectal cancer (AXEPT): a multicentre, open-label, randamised, non-inferiority, phase 3 trial. *Lancet Oncol.* 2018; **19**: 660–71.