Case Report

Targeted Therapy Based on Tumor Genomic Analyses in Metastatic Urachal Carcinoma

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Clinical Practice Points

- Urachal cancer is rare and has a prevalence of approximately 0.2%.
- In the setting of metastatic disease, chemotherapy has been used with some success. However, there is no standard chemotherapy regimen. Once chemotherapy fails, treatment options are limited.
- To date, there are a limited number of case reports regarding the use of targeted agents empirically, none of which were based on actionable mutations identified through tumor genomic profiling.
- In this case series, we report 2 patients with metastatic urachal cancer who were treated with targeted agents (sorafenib, sunitinib, and trametinib) based on actionable mutations found from their tumors, resulting in clinical response for 1 of the patients. The second discontinued therapy owing to adverse effects from the agent before disease response could be assessed.
- We propose that, for patients in whom standard of care chemotherapy have failed, genomic testing for actionable mutations should be considered to guide subsequent therapy selection.

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Introduction

Urachal cancer is rare, with a prevalence of approximately 0.2%[1,2]; it arises from the fibromuscular band that connects the dome of the bladder and the umbilicus.[3] Localized urachal cancer is treated with curative-intent surgical resection. Metastatic disease typically involves the lungs, lymph nodes, bone, intestines, brain, and liver and is generally not amenable to definitive resection.[1] Given the rarity of this condition, no large prospective trials have been conducted to evaluate systemic treatment. However, the use of chemotherapy in the metastatic setting has proven effective in some cases.[4] Once chemotherapy fails, options are limited. We hereby report 2 cases of metastatic urachal cancer treated with targeted agents selected based on the presence of actionable mutations identified through tumor genomic profiling.

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Case 1

A 42-year-old female with type II diabetes mellitus and hypothyroidism presented with lower abdominal pain. A computed tomography (CT) of the abdomen and pelvis revealed an infected urachal cyst connected to the bladder, which was drained and treated with antibiotics. Three months later, she underwent excision of the urachal remnant cyst with partial cystectomy and was found to have a large mucinous tumor (pT3b) involving approximately half of the 8 cm urachal cyst. She subsequently underwent bilateral pelvic lymph node dissection. Pathology of the tumor was consistent with mucinous adenocarcinoma invading the bladder wall and perivesical fibroadipose tissue with involvement of 1 of 21 lymph nodes (stage IVA based on Sheldon staging, pT3bN1M0 or Stage IV based on TNM staging). She received 12 cycles of adjuvant chemotherapy with 5-fluorouracil (5-FU) and irinotecan (FOLFIRI). One year later, she developed bilateral pulmonary nodules. Biopsy showed metastatic urachal carcinoma, positive for the *G12D* mutation (*C. 35G > A*) in the *KRAS* gene. Thereafter, she received chemotherapy regimens including FOLFIRI (7 months), single-agent capecitabine (4 months), gemcitabine and cisplatin with (9 months) and without 5-FU (7 months), paclitaxel with methotrexate, and cisplatin (1 month) with variable duration of response.

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After several lines of chemotherapy, the tumor recurred locally in her bladder and metastasized to her sigmoid colon. The recurrent tumor in the bladder was resected and sent to Foundation One Medicine for next generation sequencing. Mutations were identified in *GNAS R201H, KRAS G12D*, and *TP53 R273H*. She was started on trametinib 2 mg daily, based on the finding of *GNAS* and *KRAS* mutations. Trametinib was discontinued after a month owing to worsening dyspnea with mild reduction in her left ventricular ejection fraction and development of pulmonary hypertension (grade 3 adverse events based on the National Cancer Institute Common Toxicity Criteria version 4.0).[5] Her disease progressed a month after discontinuation of trametinib. Three cycles of paclitaxel were subsequently administered, complicated by sepsis. She expired shortly thereafter, 6 years after her initial diagnosis of urachal carcinoma and 3 years after she was found to have metastatic disease.

Case 2

A 60-year-old female with type II diabetes mellitus and hypertension presented with hematuria. Cystoscopy revealed an ulcerated mass at the dome of the bladder. Biopsy demonstrated invasive, moderately differentiated adenocarcinoma. A CT of the chest, abdomen, and pelvis and a bone scan did not reveal evidence of metastases. She underwent a partial cystectomy, urachectomy, and bilateral lymph node dissection. Pathology showed adenocarcinoma, and it was suggestive of urachal origin rather than bladder, based on the location at the bladder dome, enteric histology, presence of urachal remnant, and no other sites of involvement. The tumor measured 1.8 cm; there was no lymph node involvement (stage IIIA based on Sheldon staging, pT3bN0M0 or Stage 3 based on TNM staging), and surgical margins were positive. She received 8 cycles of adjuvant FOLFIRI.

Approximately 3.5 years after her initial surgery, a CT of the abdomen and pelvis showed 2 new enhancing left abdominal soft tissue masses measuring 2.9 cm × 2.7 cm and 1.8 cm × 2.4 cm, respectively. One of these masses was resected, and pathology revealed adenocarcinoma consistent with her previous primary urachal adenocarcinoma. Next generation sequencing of her metastases was performed, and genomic alterations were identified in *MAP2K1 K57N*, *TP53 R273C*, and *BCOR K839fs*5*, as well as *FLT3* and *CDK8* amplifications. She began sorafenib 200 mg daily based on *FLT3* mutation but was discontinued 4 weeks later after development of a diffuse skin rash (grade 3 adverse event). She then began trametinib 2 mg daily to target the *MAP2K1* mutation. Imaging studies revealed stable disease by Response Evaluation Criteria In Solid Tumors criteria. Ten months later, a CT of the abdomen and pelvis showed stable left abdominal mass but interval development of a new lesion of the right adnexal area measuring 12.7 cm × 8.0 cm. Owing to disease progression, she was switched to sunitinib 37.5 mg daily. Restaging scans after 2 months showed that her right adnexal mass increased in size, but the left abdominal mass was no longer present. In view of this mixed response, she underwent excision of the right adnexal mass, left oophorectomy for a possible mass, and sub-total omentectomy. Two months later, she was found to have a new left pelvic mass suspicious for recurrent tumor. At the time of this writing, she has not been started on further systemic treatments given delayed healing of her abdominal wound, which is actively being managed.

Discussion

Metastatic urachal carcinoma is commonly treated with systemic chemotherapy. Owing to the absence of prospective randomized trials, the choice of chemotherapy agents used is based on case reports and case series, extrapolating from regimens commonly used for colorectal adenocarcinoma, given the similarities in morphology, and urothelial carcinoma. Examples of chemotherapy combinations resulting in at least stable disease or partial/complete responses are shown in Table 1. To date, only 1 publication has reported the use of targeted therapy used as empiric treatment in a patient with metastatic urachal carcinoma after failing 2 lines of systemic chemotherapy.[16] In this case, the patient had stable disease that lasted for 5 months after starting a tyrosine kinase inhibitor, sunitinib. To our knowledge, there are no published reports of the use of targeted therapy for metastatic urachal cancer based on predisposing genomic alterations in the tumor. In our case series, we report 2 patients with metastatic urachal carcinoma who were treated with targeted therapy based on the presence of actionable mutations.

Owing to the rarity of this condition, studies on the genetic alterations in urachal carcinoma are limited. Since urachal carcinoma appears morphologically similar to colorectal carcinoma (CRC), Sirintrapun et al. studied the presence of microsatellite instability, *KRAS*, and *BRAF* mutations (present in 15%, 42%, and 15%, respectively, in patients with CRC) in 7 patients with high stage (pT3a-pT4b based on Sheldon staging) urachal cancer.[17-19] One patient had histology of "enteric, otherwise not specified," the rest were mucinous; 4 cases also had additional signet ring features. Two and 3 patients, respectively, demonstrated evidence of microsatellite instability (1 with mutS homolog 2 and mutS homolog 6 loss, 2 with postmeiotic segregation increased 2 loss) or *KRAS* mutations at codon 12. *KRAS* mutation and MSI were mutually exclusive; none of the cancers were *BRAF*-mutated. Compared with patients without *KRAS* mutations, the overall survival was higher in patients if the mutations were present (6.5 months vs. 101.7 months). None

Table 1 Published Chemotherapeutic Regimens Used for Metastatic Urachal

Chemotherapy Regimens
5-FU, gemcitabine, and cisplatin[4]
5-FU, doxorubicin, and mitomycin-C[6]
5-FU, irinotecan, with or without bevacizumab[7,8]
5-FU, doxorubicin, plus etoposide[9]
5-FU, cisplatin, and α-interferon[4,9]
5-FU, cisplatin, ifosfamide, and etoposide[10]
5-FU, cisplatin, methotrexate, and epirubicin[11]
Capecitabine, irinotecan, and oxaliplatin[16]
Cisplatin, ifosfamide, and paclitaxel[12]
Cisplatin, doxorubicin, and mitomycin, followed by maintenance uracil and ftorafur[9]
Cisplatin, methotrexate, vinblastine, and doxorubicin[4]
Cisplatin and S1[13,14]
Carboplastin and paclitaxel[3]
Irinotecan single agent[15]

Abbreviation: 5-FU = 5-Fluorouracil.