CASE REPORT

Case Report: Good responsiveness of metastatic sarcomatoid urothelial carcinoma with chondrosarcomatous differentiation to immune checkpoint inhibitor after radical surgery and adjuvant chemotherapy [version 1; peer review: 1 approved]

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Abstract

Background: Sarcomatoid urothelial carcinoma with chondrosarcomatous differentiation (SUCCD) in the ureter has a poor prognosis and is a rare histological variant of ureteral cancer. The majority of ureteral cancers are urothelial carcinomas.

Clinical case: We present a case of well-controlled metastatic SUCCD treated with an immune checkpoint inhibitor after radical surgery and failed adjuvant chemotherapy. The patient was a 68-year-old male with previous cure history of cT1 staged esophageal squamous cell carcinoma referred to the urology department for a right hydronephroureterosis complicating an intraureteral enhancing mass. After ureteroscopic biopsy and intraureteral urine cytology, atypical pleomorphic cell nests and chondroid tissue consistent with sarcomatoid urothelial carcinoma were observed. The patient underwent a successful radical right nephroureterectomy with bladder cuffing. The final diagnosis was a pT3N0 sarcomatoid urothelial carcinoma (heterologous component: chondrosarcoma > 95%) located at the right distal ureter and right renal calyx with infiltration of the periureteric fat and renal parenchyma of the renal capsule. On the postoperative one-month follow-up computed tomography scan, multiple enlarged lymph nodes and metastatic lung nodules were detected. The initiated adjuvant three cycles of gemcitabine-caboplatin therapy was marked by disease progression;
thus, second-line therapy with atezolizumab was used for treatment. After five cycles of atezolizumab, the tumors showed a partial response without any grade 3 complications.

**Conclusion:** The recurrent metastatic SUCCD showed good response to the immune checkpoint inhibitor after unsuccessful therapy with radical surgery and first line chemotherapy despite the unfavorable outcome of the pathology.

**Keywords**
urothelial carcinoma, sarcoma, chondrosarcoma, immune checkpoint inhibitor, atezolizumab
Introduction

Ureteral cancer is rare, with a prevalence of less than 10% of all urinary tract urothelial carcinomas. Most (>90%) urothelial carcinomas occurring in the ureter are transitional cell carcinomas, while the others (<10%) include sarcomatoid urothelial carcinoma, squamous cell carcinoma, adenocarcinoma, and small cell carcinoma. Among the rare histology types, urothelial carcinoma with chondrosarcomatous differentiation is the most rare. A recent review by Lu et al. showed a poor survival outcome in 25 sarcomatoid ureter cancer cases with chondrosarcomatous differentiation. In this case study, we present a 68-year-old patient recently diagnosed with sarcomatoid urothelial carcinoma with chondrosarcomatous differentiation discovered during esophageal cancer treatment. We thereby report a case of good response to the immune checkpoint inhibitor with an overall review of the histopathological characteristics of sarcomatoid ureteral cancer with some genetic background.

Case description

A 68-year-old male patient was referred to the urology department for right hydronephrosis complicating an incidental distal ureter stricture, which was found during an abdominal computed tomography (CT) scan for distal esophageal cancer. The patient was recently diagnosed with a 1.2 cm round-shaped distal esophageal squamous cell carcinoma, clinically stage T1, and was receiving a two-week 6600 cGy proton therapy in 33 fractions. The patient had a past medical history of restrictive lung disease, alcoholic liver cirrhosis (Child A), and was a heavy ex-smoker.

The CT treatment-planning scan showed right hydronephroureterosis due to distal ureteral stricture and ureter kinking. A CT urography was further performed at the urology department showing an abnormal ureteral kinking lesion with a distal intraureteral enhancing mass, just above the ureterovesical junction of the bladder (Figure 1A). Ureteral cancer was suspected given the findings in the right distal ureter: irregular wall thickening, and hydronephrosis with multiple small stones. Cystoscopy and microscopic urine analysis using the Nuclear Matrix Protein 22 test showed negative findings, except for benign hyperplasia of the prostate and a moderate trabeculated bladder without any voiding symptoms. Further, ureteroscopic biopsy with intraureteral urine cytology under general anesthesia found atypical cells, atypical pleomorphic cell nests, and chondroid tissue, consistent with sarcomatoid urothelial carcinoma (Figure 1B).

After the first two-week proton therapy, the patient underwent a successful right open radical nephroureterectomy from the 11th intercostal incision and pelvic Gibson incision for bladder cuffing without a positive resection margin and intratumoral positive lymph nodes. Macroscopically, the pelvocalyxx was enlarged, and the cut surface revealed multiple whitish solid tumors measuring up to 2.1 × 1.7 × 1.3 cm in the pelvis and extending to the cortex. The tumor also involved the distal ureter (Figure 2A). Microscopically, the tumor had a biphasic appearance of a high-grade urothelial carcinoma and a sarcomatous component with chondrosarcomatous differentiation (Figure 2B). Immunohistochemical analysis indicated that the sarcomatous areas were positive for vimentin, and the areas of malignant urothelial cells were diffusely positive for pan-cytokeratin and p63 (Figure 2C). Based on the histological and immunohistochemical findings, a pT3N0 sarcomatoid urothelial carcinoma (heterologous component of chondrosarcoma >95% positive for vimentin, p63, and pan-cytokeratin) was diagnosed. The tumor in the renal calyx infiltrated the periureteric fat and renal parenchyma of the renal capsule.

The patient was discharged within 10 days without any complication including azotemia and resumed the two-week proton therapy for esophageal cancer. On the postoperative one-month follow-up CT scan, an increased size and necrosis of aortocaval lymph nodes and multiple metastatic lung nodules were detected. Three cycles of adjuvant gemcitabine and carboplatin (gemcitabine 1000mg/m² D1, 8, and carboplatin AUC 5 D1, every 3 weeks) chemotherapy was administered due to the decreased renal function because of an underlying chronic kidney disease.

Figure 1. (A) Preoperative CT urography and (B) ureteroscopy findings.
The follow-up imaging after 3 cycles (9 weeks) of the initial treatment regimen indicated disease progression; thus, a second-line systemic therapy was initiated using an immune checkpoint inhibitor, atezolizumab (1200mg, every 3 weeks). After three cycles of atezolizumab, the multiple enlarged lymph nodes and lung nodules were no longer enlarged, and after five cycles of atezolizumab the overall size of multiple metastatic lesions decreased (Figure 3), indicating a partial response to atezolizumab. The patient has undergone seven cycles of atezolizumab without any grade 3 adverse event, and will continue to be treated.

Discussion

Chondrosarcoma is one of the most common malignant bone tumors in adults. Chondrosarcomas are further stratified into conventional, mesenchymal, dedifferentiated, and clear cell subtypes. The conventional chondrosarcoma represents about 85% of all chondrosarcomas and is notoriously difficult to treat with chemotherapy. According to the 4th edition of the World Health Organization Classification of Tumors, the International Agency for Research on Cancer defined the sarcomatoid variants of urothelial carcinoma as being histologically indistinguishable from those of sarcomas with a prevalence of 0.6% of all bladder tumors. The most common symptom of SUCCD is gross hematuria with male predominance (ratio 3:1). The aggressive pathologic feature results in mostly nodal and visceral metastases at the time of diagnosis, like in our case. Our patient had an underlying alcoholic liver cirrhosis, a chronic pulmonary disease, and a distal esophageal cancer being treated with radiation therapy. He was diagnosed with pT3NxM0 chondrosarcoma with multiple sites at the distal (pT2) and the proximal ureter (pT3). Our case was similar to a surgical case of an 81-year-old Japanese female with a multifocal, synchronous pT2 sarcomatoid ureteral cancer and pT3 renal pelvic urothelial carcinoma with multiple visceral metastases diagnosed on postoperative month 11. Our patient had no nodal enlargement or metastases at the time of preoperative workups; however, the lung metastases and multiple nodal enlargement observed on postoperative month one strongly support the speculation that micrometastases were already present at the time of diagnosis of the right hydronephroureterosis and surgery. It is also worth noting that our patient presented with multiple gross hematurias during the esophageal cancer workups, and the right atrophic kidney with cystic changes and hydronephrosis were suggestive of a long-existent tumor.

The prognosis of SUCCD is dismal (3–24 months survival time) because the majority of urothelial carcinoma cases with sarcomatoid differentiation are known to be high grade, with an increased risk of micrometastases at the time of diagnosis due to late diagnosis, and have challenges associated with diagnosing a rare multifocal ureteral cancer. Therefore, surgical resection is the primary treatment choice especially for chemoradiation-resistant tumors despite diagnosis at advanced stages. However, several retrospective case series and clinical trials have proposed the use of either anti-angiogenic inhibitors or immune therapy in the current genetic era. Immunotherapy has had enormous success in treating multiple cancer subtypes. Success has been particularly seen with immune checkpoint inhibitors, which are now approved as standard therapy in melanoma, lung cancer, and genitourinary cancers. Immunotherpay agents are increasingly demonstrating success in many cancer subtypes, and there have been preclinical suggestions that they may do the same in chondrosarcoma. The PI3K-Akt-mTOR, SRC, and Hedgehog pathways are the potential oncogenic targets for chondrosarcoma with VEGF2 inhibitors. Other identified targets with next-generation sequencing are recurrent alterations in TP53, ACVR2A, COL2A1, YEATS2, and IDH. These play a role in chondrosarcoma; therefore, they could be potential targets for immunomodulatory agents. In addition, immune checkpoint inhibitors have been
successful treatments for sarcomas. Atezolizumab, an immune checkpoint inhibitor, has been approved for second-line therapy in ureteral cancer in Korea and in our case we observed a good response. A previous 67-year-old male patient treated with four cycles of nivolumab resulted in a near-complete response in metastatic pulmonary nodules\textsuperscript{13}. Immune checkpoint inhibitors have been suggested to provide tumor-specific immune responses against cancer-specific antigens such as NY-ESO-1 or LAGE-1 in sarcoma patients with dedifferentiated chondrosarcoma, as well as chondrosarcoma cell lines\textsuperscript{13–15}. The expected favorable outcome with the use of a single agent PD1 inhibitor with/without immunomodulatory agents in chondrosarcoma needs to be further investigated.

In conclusion, this recurrent metastatic case of carcinoma is a rare variant of multifocal synchronous ureteral cancers which responded well to atezolizumab. Our findings will help in early diagnosis, treatment planning, and better management with immune checkpoint inhibitors in case the current chemotherapy fails; thus, ensuring improved prognoses. In future, a series of case reports and studies would highlight the clinical benefit of checkpoint inhibitors with/without immunomodulatory agents in this disease clearly.

**Ethical considerations and consent**

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient and the caregiver of the patient.

This retrospective study was approved by the Institutional Review Board (IRB) of the National Cancer Center (IRB No. NCC 2020- 0313-0001). This case report was proceeded in accordance with the tenets of the ethical guidelines and regulations of the World Medical Association Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects.

**Data availability**

All data underlying the results are available as part of the article and no additional source data are required.

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In this study, they presented a case of sarcomatoid urothelial carcinoma with chondrosarcomatous differentiation in the ureter treated with an immune checkpoint inhibitor after radical surgery and failed adjuvant chemotherapy. They showed that immune checkpoint inhibitor might be a successful option in case the current chemotherapy failed. Congratulations on good and inspiring work. It is pleasure to review high quality cases.

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Is the background of the case's history and progression described in sufficient detail? Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes? Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment? Yes

Is the case presented with sufficient detail to be useful for other practitioners? Yes

Competing Interests: No competing interests were disclosed.
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