Sarcomatoid urothelial carcinoma with chondrosarcomatous differentiation of the ureter: A case report and review of the literature

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Abstract. Sarcomatoid urothelial carcinoma of the urinary tract is associated with poor prognosis. The majority of sarcomatoid urothelial carcinomas are found in the urinary bladder, while a small minority have been shown to arise from the ureter. In the present case, a 72-year-old male patient was diagnosed with sarcomatoid urothelial carcinoma with chondrosarcomatous differentiation of the left ureter, and subsequently underwent nephroureterectomy and retroperitoneal lymph node dissection. Two lymph nodes from the renal hilum and one paraaortic lymph node were also found to have metastatic involvement; however, the patient refused to receive chemotherapy or radiotherapy and succumbed to bone and omentum metastasis at 6 months after the initial diagnosis. Sarcomatoid urothelial carcinoma of the ureter is uncommon. Even rarer is the presence of malignant heterologous elements, such as chondrosarcoma. The present study reports a rare case of sarcomatoid urothelial carcinoma with chondrosarcomatous differentiation of the ureter, as well as a review of the literature, in order to demonstrate the aggressive nature of this particular malignancy.

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Introduction

Sarcomatoid urothelial carcinoma is an uncommon histological variant of urothelial carcinoma. The majority of sarcomatoid urothelial carcinomas are found in the urinary bladder (1). Generally, >90% of ureteral tumors are urothelial carcinomas; other types of ureteral tumors, including squamous cell carcinoma, adenocarcinoma and small cell carcinoma, are less common (2). To the best of our knowledge, only 24 cases of the ureteral sarcomatoid urothelial carcinoma have been reported in the PubMed database (http://www.ncbi.nlm.nih.gov/pubmed) (Table I) (3-24), the majority of which were accompanied by a malignant heterologous element (chondrosarcoma). Sarcomatoid carcinoma of the urinary bladder has been associated with a poor prognosis (25). Due to the rarity of this tumor, there is limited information regarding its pathological features, clinical behavior and prognosis.

The present study reports a rare case of sarcomatoid urothelial carcinoma with chondrosarcomatous differentiation of the ureter. In addition, the clinical and pathological features of ureteral sarcomatoid carcinomas, with particular emphasis on the differential diagnosis and prognosis of the disease, are discussed based on a review of the existing literature. Written informed consent was obtained from the patient.

Case report

A 72-year-old male patient presenting with hematuria, urinary irritation and pain in the left flank and groin was referred to Sun Yat-Sen University Cancer Center (Guangzhou, China) on March 5, 2013. The patient had undergone a cystoureteroscopy at Jieyang People's Hospital (Jieyang, China) on February 27, 2013, and poorly differentiated urothelial carcinoma had been detected on the ureteral biopsy. He subsequently presented to our hospital. The patient had a history of kidney calculi for ~10 years, tobacco smoking for ~40 years and unknown drug allergies. His family had no notable medical history. Laboratory examinations showed the following: White blood

Table I. Reported cases of sarcomatoid urothelial carcinoma of the ureter.

Author (year)	Age (years) /gender	Symptoms/ clinical findings	Tumor histology	Outcome	Reference
Renner (1931)	71/M	Unknown	Papillary carcinoma, SCT, chondrosarcoma	Unknown	(3)
McDade *et al* (1974)	66/M	Hematuria, colic-like abdominal pain	Malignant epithelial and stromal elements	Local recurrence 4 months later; treatment with diathermy; patient was symptom-free at time of publication	(12)
Yano *et al* (1984)	66/M	Flank pain, intermittent fever	SQCCA, SCT, chondrosarcoma	Succumbed to disease 2 years later; autopsy showed recurrence of sarcomatous component (chondrosarcoma)	(4)
Bryard *et al* (1987)	75/F	3-week history of urinary frequency, left flank pain and fever	Urothelial carcinoma, SQCCA, adenocarcinoma, chondrosarcoma	Local recurrence 6 months later with left iliac paraaortic lymph node metastasis; succumbed to disease 2.5 years later	(5)
Fleming *et al* (1987)	68/M	6-year history of mild difficulty initiating micturition and urinary frequency; loin pain, single episode of hematuria	Pleomorphic carcinoma, SCT	Pedunculated mass in the bladder measuring 6 cm arising from right ureteral stump 6 months later; succumbed to widespread metastasis	(24)
Fukuda *et al* (1991)	69/M	Hematuria and hydronephrosis	Urothelial carcinoma, SQCCA, SCT, chondrosarcoma	Patient alive at time of publication	(6)
Tsutsumi *et al* (1993)	60/M	Asymptomatic gross hematuria	SCCA, urothelial carcinoma, SQCCA, LMS, chondrosarcoma	Recurrence of high-grade invasive transitional cell carcinoma on bladder neck 8 months later; radiation and chemotherapy treatment; back pain 4 months later due to thoracic vertebra metastasis; no evidence of metastasis 16 months s/p primary diagnosis and subsequent radiation	(7)
Ishikura *et al* (1994)	73/M	Computed tomography revealed a solid, cystic mass in the left retroperitoneum and multiple nodules in the liver	Undifferentiated carcinoma, blastomatous cells, chondrosarcoma	Large recurrent tumor filling the abdomen s/p surgery and chemotherapy; succumbed to disease 3 months later	(8)
Murata *et al* (1994)	80/M	Edema in right lower extremity	SQCCA, MFH-like SCT	Succumbed to disease 3 months after diagnosis	(13)
Murata *et al* (1994)	62/M	Gross hematuria	Urothelial carcinoma, SQCCA, MFH-like sarcoma	No evidence of disease, patient alive 23 months later	(13)
Burt *et al* (1995)	74/M	Severe right-sided abdominal pain, vomiting and fever for 24 h	Urothelial carcinoma, osteosarcoma, SCT, myxoid areas	No evidence of disease, patient alive 9 months later	(14)
Nagayoshi *et al* (1997)	60/F	History of right flank pain s/p oophorectomy and radiation therapy for ovarian cancer at the age of 40 years	Urothelial carcinoma, SCT	No evidence of disease, patient alive 5 months later	(15)

Table I. Continued.

Author (year)	Age (years) /gender	Symptoms/ clinical findings	Tumor histology	Outcome	Reference
Ichiniyagi *et al* (1998)	67/F	Hematuria	Urothelial carcinoma, SQCCA, chondrosarcoma	Succumbed to disease at 10 months s/p adjuvant radiotherapy	(9)
Kakoi *et al* (2002)	89/M	Gross hematuria, left hydronephrosis caused by ureteral tumor	Carcinosarcoma of renal pelvis and ureter	Recurrent gross hematuria s/p radiation and chemotherapy; cancer-free for 1.5 years s/p left nephroureterectomy	(20)
Perimenis *et al* (2003)	68/F	Hematuria, low back pain	PD carcinoma, SCT	Pelvic recurrence at 18 months with liver metastasis 2 months later; succumbed to disease 2 years later	(16)
Johnin *et al* (2003)	58/F	Painless hematuria	Urothelial carcinoma, osteosarcoma and chondrosarcoma	Tumor recurrence in bladder 2 months later; succumbed 6 months after presentation, due to local recurrence despite anterior exenteration	(23)
Lee *et al* (2004)	90/F	Left iliac fossa pain	Malignant SCT	The patient refused treatment and succumbed to the disease 3 months after diagnosis	(17)
Petsch *et al* (2004)	82/F	Left flank pain	SC	Not stated	(19)
Darko *et al* (2006)	81/F	Gross hematuria	Urothelial carcinoma, SQCCA, mesenchymal chondrosarcoma	Positron emission tomography identified new nodules in the lungs and an enlarged paraaortic lymph node compressing the vena cava 4 months later; chemotherapy administered	(22)
Busby *et al* (2006)	Not stated	Unknown	SC	Recurrence in tumor bed 3 months later; adjuvant chemotherapy treatment; succumbed to disease 3 months later	(18)
Maeda *et al* (2007)	63/M	Asymptomatic gross hematuria	Basaloid SQCCA, SCT, chondrosarcoma	Uneventful postoperative course; no tumor recurrence at 10 months	(10)
Völker *et al* (2008)	83/M	Painless macrohematuria and hydronephrosis	Urothelial carcinoma, SCT, poorly differentiated transitional cell carcinoma, chondrosarcoma	No evidence of the disease; patient alive 36 months later	(11)
Völker *et al* (2008)	67/F	Hydronephrosis	Urothelial carcinoma, SCT, RMS, undifferentiated sarcoma	No evidence of the disease; patient alive 18 months later	(11)
Nicolas *et al* (2014)	63/M	Difficulty of urination for several months	Urothelial carcinoma, PD carcinoma, adenocarcinoma, SCT, chondrosarcoma	Recurrent lesions progressed despite treatment and patient succumbed to disease 16 months after initial diagnosis	(21)
Lu *et al*	72/M	Gross hematuria, urinary irritation, pain in left flank and groin	Urothelial carcinoma, SCT, chondrosarcoma	Patient refused treatment and succumbed to bone and omentum metastases 6 months later	Present case

SCT, spindle cell tumor; SQCCA, squamous cell carcinoma; SCCA, small cell carcinoma; LMS, leiomyosarcoma; MFH, malignant fibrous histiocytoma; PD, poorly differentiated; SC, sarcomatoid carcinoma; s/p, status post; RMS, rhabdomyosarcoma.

cell count, $6.7x10^9$/l (normal range, 3.5-$9.5x10^9$/l); neutrophils, 56.5% (normal range, 0.40-0.75%); red blood cell count, $4.34x10^{12}$/l (normal range, 3.8-$5.8x10^{12}$/l); hemoglobin level, 140 g/l (normal range, 110-160 g/l); platelet count, $158x10^9$/l (normal range, 100-$300x10^9$/l); red blood cells in urine, 37/μl; occult blood, 2+. The left and right renal glomerular filtration rates were 7.16 ml/min and 51 ml/min (normal range, 80-125 ml/min), respectively, and the levels of the tumor markers serum creatinine, urea nitrogen and cystatin C were found to be within the normal ranges. Ultrasonography of the urinary tract detected that the tumor was located in the middle-lower ureter, and that the lumen was obstructed by 70x15x15 mm mass, which led to the dilatation of the proximal ureter and renal pelvis (Fig. 1A and B). Sonography led to suspicion of upper tract urothelial carcinoma. Chest X-ray and ultrasonography of the urinary tract indicated no signs of metastasis.

The patient underwent left nephroureterectomy and lymphadenectomy. Macroscopically, the surgical specimen revealed a tumor located in the distal ureter. In addition, no obvious abnormalities in the renal pelvis were observed. On the cut section of the tumor, fragile areas were found on the grayish-yellow cut surface. Microscopic examination revealed that the tumor cells were arranged in sheets or tubes, or had a 'cracked' appearance (Fig. 2A and B). Atypia and pathological mitosis of cancer cells was distinct. Immunohistochemical analysis indicated positivity of the tumor cells for vimentin (monoclonal mouse antibody; cat. no. ZM-0260; ZSGB-BIO, Beijing, China; Fig. 3A), epithelial membrane antigen (monoclonal mouse antibody; cat. no. ZM-0095; ZSGB-BIO; Fig. 3B), CD10 (monoclonal rabbit antibody; cat. no. NCL-CD10-270; Quanhui Imp & Exp Int'l Co., Ltd., Macao, China; Fig. 3C), CD99 (monoclonal rabbit antibody; cat. no. ZA-0577; ZSGB-BIO; Fig. 3D) and CD56 (monoclonal mouse antibody; cat. no. ZM-0057; ZSGB-BIO), and negativity for low molecular weight cytokeratin (CK) (monoclonal mouse antibody; cat. no. Z2061; ZSGB-BIO), CK-7 (monoclonal mouse antibody; cat. no. 180234; ZSGB-BIO), carcinoembryonic antigen (monoclonal mouse antibody; cat. no. ZM-0061; ZSGB-BIO), CK5/6 (monoclonal mouse antibody; cat. no. ZM-0313; ZSGB-BIO), leukocyte common antigen (monoclonal mouse antibody; cat. no. ZM-0183; ZSGB-BIO), S100 (monoclonal rabbit antibody; cat. no. ZA-0225; ZSGB-BIO), CD34 (monoclonal mouse antibody; cat. no. ZM-0046; ZSGB-BIO), CD31 (monoclonal rabbit antibody; cat. no. ZA-0568; ZSGB-BIO), synaptophysin (monoclonal rabbit antibody; cat. no. ZA-0506; ZSGB-BIO), chromogranin A (polyclonal rabbit antibody; cat. no. ZA-0066; ZSGB-BIO) and low molecular weight CK (monoclonal mouse antibody; cat. no. ZM-0329; ZSGB-BIO). A high cell proliferation rate (>60% immunoreactive cells) was revealed by Ki-67 staining, indicating the malignant nature of the lesion. Reticular fiber staining showed that the cells had a nest-like distribution; therefore, a diagnosis of invasive sarcomatoid urothelial carcinoma interspersed with chondrosarcomatous differentiation of the ureter was proposed. The retroperitoneal lymph nodes on the left side of the renal hilum and paraaortic nodes were also involved. The patient refused to undergo chemotherapy and succumbed to bone and omentum metastases 6 months later.

Discussion

Urothelial carcinoma is the most common histological subtype of urothelial cancer, followed by squamous cell carcinoma, adenocarcinoma and small cell carcinoma. Over 90% of urothelial carcinomas derive from the urinary bladder, 8% from the renal pelvis, and the remaining 2% from the ureter and urethra (26). Urothelial carcinoma has an uncommon sarcomatoid variant with a distinctive histological appearance. 'Invasive urothelial carcinoma, sarcomatoid variant', was the term preferred by the 2004 World Health Organization Classification Tumors of the Urinary System (27). It is generally believed that sarcomatoid carcinoma is a rare type of cancer. Furthermore, the sarcomatoid component may be a metaplastic part of the cancer, and the heterologous sarcomatoid component of the tumor (such as chondrosarcoma and osteosarcoma) derives from a special type of mesenchyma (22).

With regard to the overlapping histology and immunophenotype, as well as the aggressive biological behavior of these tumors, a hypothesis was presented by the researchers that both carcinomatous and sarcomatous elements have a common cell of origin (27). This hypothesis was validated by a series of studies. Sung *et al* (28) performed a study on the loss of heterozygosity and X-chromosome inactivation, the results of which demonstrated a considerable overlapping loss of heterozygosity between the sarcomatoid and carcinomatous components, and the uniform, non-random X-chromosome inactivation is consistent with the hypothesis that sarcomatoid urothelial carcinoma of the urinary bladder is monoclonal in origin. Subsequently, Völker *et al* (11) further demonstrated considerable, but not complete, overlapping of the genetic alterations by comparative genomic hybridization of the two sarcomatoid carcinomas in their unusual location, the ureter. It was also demonstrated that the epithelial and mesenchymal components shared similar chromosomal gains and losses. These findings are consistent with the hypothesis that sarcomatoid carcinoma is developed from a common pluripotent progenitor cell, which has a potential for epithelial and mesenchymal differentiation.

Due to the aggressive nature of this neoplasm, sarcomatoid urothelial carcinoma has a considerably poor prognosis compared with the other types of ureteral cancer (21). The presence of a sarcomatoid component has been associated with a dismal prognosis and an increased risk of metastasis (21,29,30). Previously reported cases of urothelial carcinoma with sarcomatoid differentiation exhibited systemic metastasis to sites including the bone, liver, lung and lymph nodes (23,24,30). The majority of these tumors are high-grade in histology (16). Other more common and less aggressive types of tumors that occur in the ureter and differ from carcinosarcoma include carcinomas with osseous or chondroid metaplasia, carcinoma with pseudosarcomatous stroma, and sarcomatoid carcinoma (21). The histological features of the metaplastic part differ from those of the primary tumor. The epithelial component consists of transitional cell carcinoma, carcinoma *in situ*, small cell carcinoma, adenocarcinoma and squamous cell carcinoma, while the stromal component consists of chondrosarcoma, osteosarcoma and leiomyosarcoma (27). Furthermore, the spindle cells of sarcomatoid carcinoma are demonstrated by immunohistochemistry. Pseudosarcomatous stromal reactions

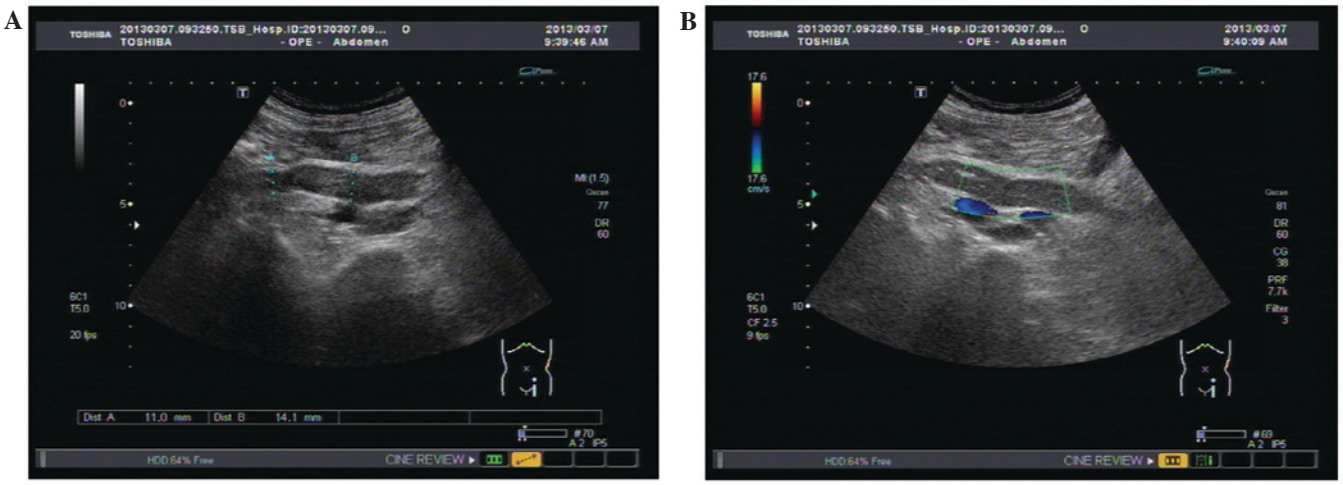

Figure 1. Ultrasound scans revealed that the mass, which was located in the middle-lower of the left ureter and measured 70x15x15 mm, exhibited (A) an iso-echo signal with (B) no distinct color doppler flow signal.

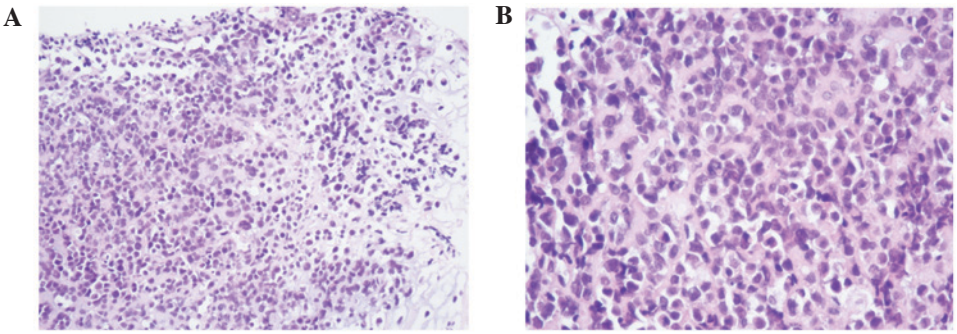

Figure 2. The ureteral urothelial carcinoma merges with the sarcomatoid carcinoma component, showing chondrosarcomatous differentiation at (A) x200 and (B) x400 magnification.

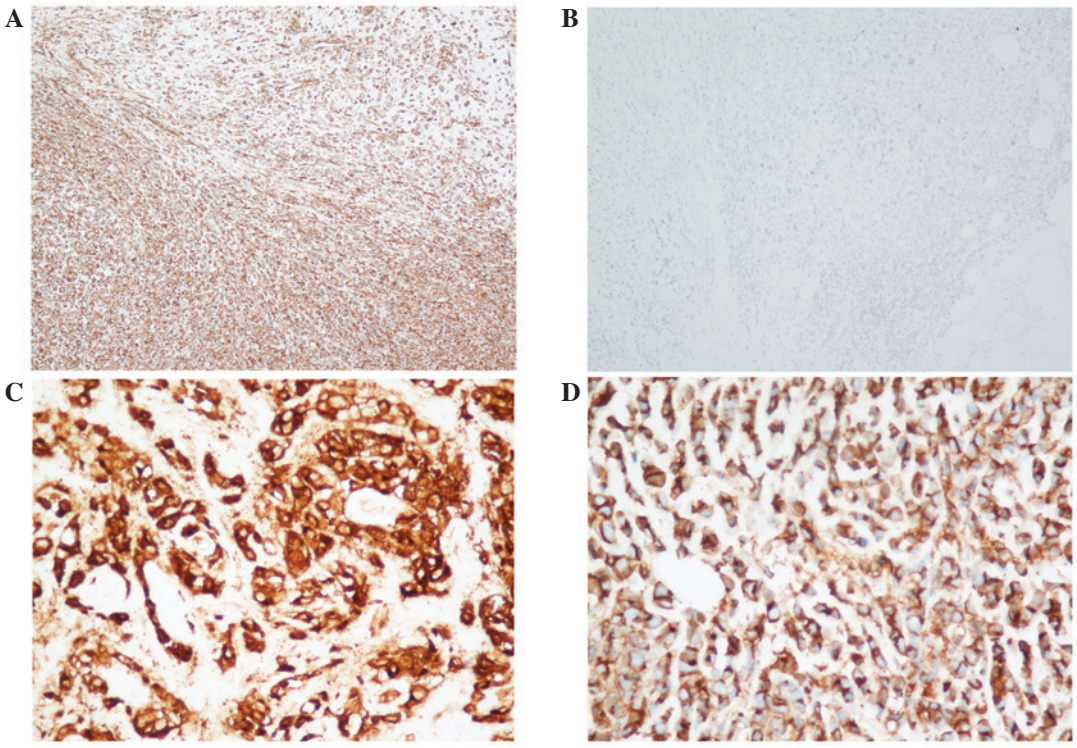

Figure 3. Immunohistochemical staining showing positivity for (A) vimentin (magnification, x100), (B) epithelial membrane antigen (magnification, x100), (C) CD10 (magnification, x400) and (D) CD99 (magnification, x200) in the cartilaginous components.

may be distinguished from carcinosarcoma by their pathological features, including lack of malignant characteristics, and display of minimal atypia and mitotic activity (31). Lichtenstein and Bernstein first described extraskeletal mesenchymal chondrosarcoma as an occurrence of the bone in 1959 (32); it was defined as a subtype of chondrosarcoma believed to arise from remnants of the metaplasia of meningeal fibroblasts or embryonic cartilage (33). Mesenchymal chondrosarcoma accounts for <1% of all sarcomas, and predominantly affects children and young adults aged 15-35 years (34). One third of cases occur outside the bone; other common sites of mesenchymal chondrosarcoma include the central nervous system, maxilla, sinuses, meninges, eyelids and thyroid (35).

Primary chondrosarcoma of the urothelial carcinoma presents a diagnostic challenge, due to its rarity, unusual location and nonspecific symptoms. Highly malignant, radiation-resistant tumors with a dismal prognosis (36) also include carcinosarcomas of the ureter, for which the optimal treatment option upon diagnosis is surgical resection; no significant improvement on the prognosis for this tumor type has been achieved by adjuvant radiotherapy or chemotherapy (16). In the present case, the patient underwent radical nephroureterectomy; however, he and his family refused to receive chemotherapy and radiotherapy to improve his general condition. Five months after surgery and 6 months after initial diagnosis, the patient succumbed to extensive bone and omentum metastases.

In conclusion, the pathological features, prognosis and treatment options for the histological variants of urothelial carcinoma differ from those of traditional urothelial carcinoma. It is important for urologists and pathologists to fully understand the features of each variant in order to improve the process of clinical diagnosis, assessment of prognosis, and, most importantly, treatment of these types of tumors.

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