Clinical Case Report

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Primary carcinosarcoma of the ureteropelvic junction associated with ureteral duplication

A case report

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Abstract

Rationale: Primary carcinosarcoma of the upper urinary tract is rare. Ureteral duplication is one of the most common urinary tract malformations. Additionally, the association between ureteral duplication and malignancy is unknown. To the best of our knowledge, no cases of malignant tumors diagnosed as carcinosarcoma with ureteral duplication have been reported. We herein report the case of a patient with carcinosarcoma of the ureteropelvic junction associated with incomplete ureteral duplication.

Patient concerns: A 60-year-old Japanese woman presented with painless gross hematuria. She had a history of total hysterectomy and chemotherapy for endometrioid carcinoma 5 years before. She had no history of occupational chemical exposure.

Diagnoses: Radiographic imaging revealed right incomplete ureteral duplication, hydronephrosis, and a polypoid tumor in the ureteropelvic junction of the lower moiety of the right kidney. Urine cytology showed a small amount of degenerated atypical epithelial and nonepithelial cells. The transureteral biopsy specimen showed dysplastic urothelial cells and atypical myoid spindle cells. These findings were indefinite for malignancy.

Interventions: The patient underwent right nephroureterectomy. Pathological examination of the resected tumor showed a biphasic neoplasm composed of carcinomatous and sarcomatous components. The sarcomatous component was immunohistochemically positive for vimentin, desmin, h-caldesmon, and α-SMA and negative for pancytokeratin (AE1/AE3), low molecular weight cytokeratin (CAM 5.2), EMA, E-cadherin, GATA3, uroplakin 2, and p63. Based on these findings, we diagnosed the tumor as carcinosarcoma.

Outcomes: The postoperative course was uneventful. No additional therapy was administered. The patient has remained alive without recurrence for 21 months since surgery.

Lessons: Carcinosarcoma can arise from ureteral duplication. Although the majority of carcinosarcomas of the upper urinary tract are diagnosed at an advanced stage and have a poor prognosis, some can have a less aggressive course. Further studies are needed to determine the association between ureteral duplication and malignancy.

Abbreviations: CT = computed tomography, UPJ = ureteropelvic junction.

Keywords: carcinoma, carcinosarcoma, cytology, leiomyosarcoma., pelvis, ureter, ureteral duplication

1. Introduction

Carcinosarcoma is a biphasic neoplasm with mixed malignant epithelial and mesenchymal components whose definition and histogenesis have long been discussed.[1–9] This neoplasm is highly aggressive in general and is often associated with poor prognosis. Carcinosarcoma is rare but can occur in a variety of organs or systems, such as the uterus, ovary, lung, breast, esophagus, and urinary tract. For the urinary tract, the majority of reported cases of carcinosarcomas are cases of the lower urinary tract, predominantly located in the urinary bladder. Several clinicopathological studies with a series of carcinosarcoma cases of the urinary bladder have been published.[8–11] In contrast, there have been only approximately 20 cases of carcinosarcoma of the upper urinary tract reported to date. Due to its rarity, the clinicopathological features of carcinosarcoma of the upper urinary tract remain incompletely elucidated.

Ureteral duplication is one of the most common urinary tract malformations found in approximately 0.8% of autopsy series.[12] There are 2 subtypes of duplicated ureter; complete

Editor: N/A.

This study was supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (No. 16K11158 to H.O.).

The authors declare that there are no conflicts of interest.

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Medicine (2019) 98:32(e16643)

Received: 21 March 2019 / Received in final form: 27 May 2019 / Accepted: 8 July 2019

http://dx.doi.org/10.1097/MD.0000000000016643

ureteral duplication refers to 2 separate ureters with 2 separate orifices in the bladder, while incomplete ureteral duplication refers to 2 ureters joining together to form a single ureter before entering the bladder. Embryologically, complete ureteral duplication occurs when 2 separate ureteric buds arise from the mesonephric duct, while incomplete ureteral duplication is caused by premature bifurcation of a single ureteric bud prior to fusion with metanephros.[13] Complications of ureteral duplication include urinary reflux, ureterocele, and ureteral obstruction.[12,14] However, the association between ureteral duplication and malignancy remains unclear.

Herein, we report a rare case of carcinosarcoma arising from the ureteropelvic junction (UPJ) of incomplete ureteral duplication. Informed consent for publication of this case report has been obtained from the patient. We also discuss the significance of distinguishing carcinosarcoma from another related entity and review the relevant literature.

2. Clinical summary

A 60-year-old Japanese woman presented with a several-day history of gross hematuria. She had no fever or pain. She had a history of total hysterectomy and postoperative adjuvant chemotherapy (paclitaxel and carboplatin) for endometrioid carcinoma (G1, pT1bN0) 5 years before. A preoperative CT scan revealed right unilateral incomplete ureteral duplication. Two months after the surgery, right hydronephrosis, which was not preoperatively present, was detected on CT scan, probably because of the ureteral stricture caused by postoperative scarring. A double-J ureteral stent was inserted and remained in place for 11 months. She developed pyelonephritis several times during the placement of the stent. One year and 7 months after the surgery, wall thickening at the UPJ of the lower moiety of the right kidney was observed on CT scan. Two years and 7 months after the surgery, a 6 mm polypoid nodule was detected at the right lower UPJ, whose size increased to 9 mm a year later. There were no signs of recurrence of endometrioid carcinoma. She also had histories of Wolff-Parkinson-White syndrome, splenectomy for thrombocytopenic purpura, glaucoma, hypercholesterolemia, and carpal tunnel syndrome and was a hepatitis B virus carrier. She had a 7-year history of smoking 10 cigarettes per day. She denied any occupational chemical exposure. She had no family history of urinary tract malignancy.

Retrograde pyelography showed right incomplete ureteral duplication, hydronephrosis, and a filling defect at the right lower UPJ (Fig. 1A). A contrast-enhanced CT scan revealed a round, uniformly enhanced polypoid tumor 12 mm in diameter (Fig. 1B), which was 3 mm larger than that observed a year before. Cystoscopy showed no tumor in the bladder. Ureteroscopy revealed a nodular tumor at the right lower UPJ. Urine cytology showed a small amount of degenerated atypical epithelial and nonepithelial cells, which were indefinite for malignancy (Fig. 2). Following cytology, the transureteral biopsy specimen showed dysplastic urothelial cells and atypical spindle cells. The atypical spindle cells were immunohistochemically positive for desmin and h-caldesmon, suggesting that there was a neoplasm with smooth muscle differentiation. With high suspicion of clinical malignancy, right nephroureterectomy was performed. The postoperative course was uneventful. The patient was followed up without additional therapy and remained alive without evidence of local recurrence or metastasis 21 months after the surgery.

3. Pathological findings

The tumor fell off of the UPJ during the surgical procedure and was submitted separately from the nephroureterectomy specimen for pathology (Fig. 3). Macroscopically, the tumor was 14 × 10 mm in size and had a spherical shape with a smooth surface. It had no stalk, which made it difficult to identify the attachment site to the ureteral wall. The cut surface showed a solid, yellowish-white appearance with hemorrhage.

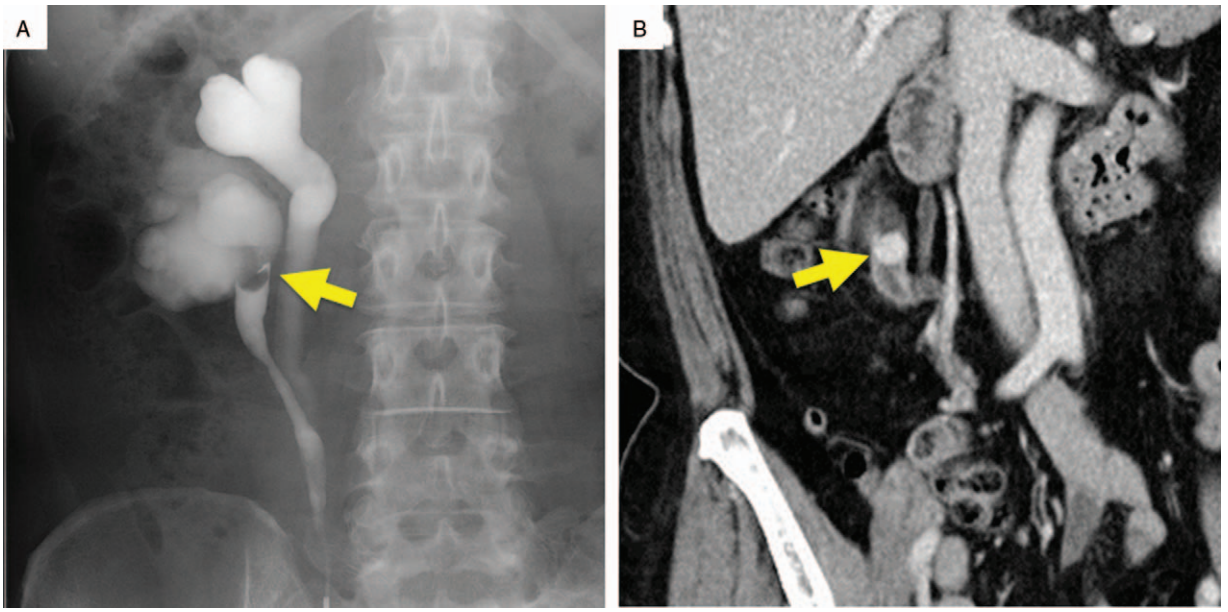

Figure 1. Radiographic imaging of the tumor. (A) Right retrograde pyelography showed incomplete ureteral duplication, hydronephrosis, and a filling defect at the ureteropelvic junction of the lower moiety (arrow). (B) Enhanced CT (coronal view) shows a round, uniformly enhanced polypoid tumor protruding into the lumen (arrow). Mild ureteral wall thickening was also observed immediately distal to the tumor.

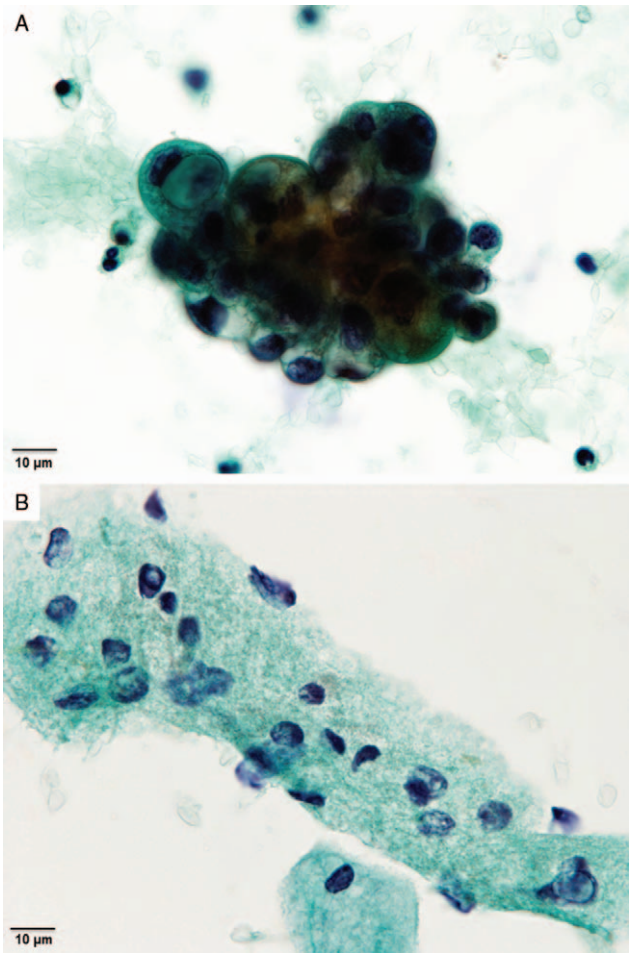

Figure 2. Photomicrographs of catheter urine cytology. (A) A small, atypical glandular-like epithelial cell cluster with mildly enlarged, hyperchromatic, irregularly shaped nuclei. (B) A small, atypical nonepithelial cell cluster with ill-defined cell borders, anisokaryosis, and mildly hyperchromatic, irregularly shaped nuclei.

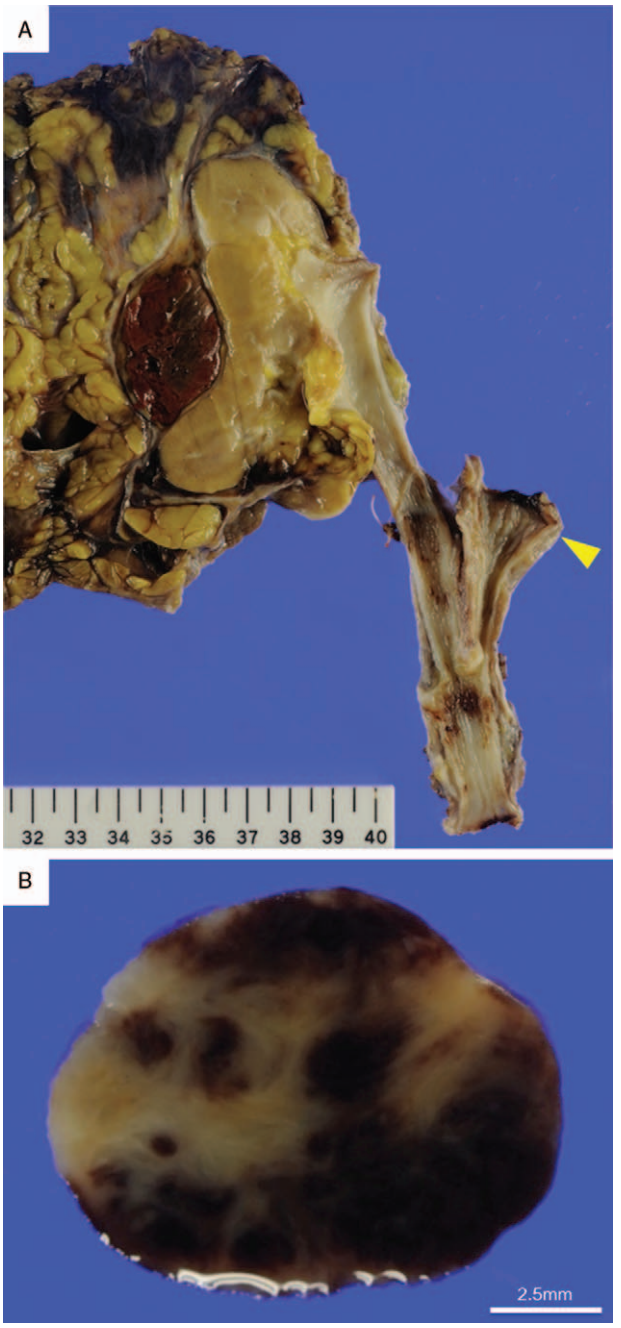

Figure 3. Macroscopic findings of the resected specimen. (A) Gross findings of the nephroureterectomy specimen. The ureter showed incomplete duplication and dilation. Tumors were not observed on the ureteral wall because they fell off during the surgical procedure. The original location of the tumor is likely to be the more severely dilated ureter (arrowhead). The distal part of the ureter was not resected because of firm adhesion to the surrounding tissue. (B) Cut surface of the tumor that fell off of the ureteral wall, showing a solid, yellowish-white appearance with hemorrhage.

Microscopically, the tumor consisted of two components: carcinomatous and sarcomatous components (Fig. 4). The tumor predominantly consisted of the sarcomatous component, which exhibited proliferation of atypical spindle cells with fibrous cytoplasm and enlarged, hyperchromatic, irregularly shaped nuclei (Fig. 4I). The surface of the tumor was covered with atypical epithelial cells with enlarged, hyperchromatic, irregularly shaped nuclei, which formed irregular glandular structures, suggestive of adenocarcinoma (Fig. 4B and C). A few nests of carcinomatous components were also observed inside the tumor (Fig. 4D and E). Some of the carcinomatous components had intercellular bridges, suggesting squamoid differentiation. There was no obvious "transition" between the 2 components.

The immunohistochemical findings of the tumor are summarized in Table 1. The carcinomatous component was positive for pancytokeratin (AE1/AE3; Leica Biosystems; Tokyo, Japan), low molecular weight cytokeratin (CAM 5.2; Becton Dickinson; San Jose, CA, USA), EMA (E29; Roche Diagnostics; Tokyo, Japan), E-cadherin (NCH-38; Nichirei Biosciences; Tokyo, Japan), GATA3 (L50-823; Biocare Medical; Pacheco, CA, USA), uroplakin 2 (BC21; Biocare Medical) (focal) and p63 (4A4; Nichirei Biosciences; Tokyo, Japan) (focal) and negative for vimentin (V9; Roche Diagnostics; Tokyo, Japan), desmin (D2-R-11; Leica Biosystems; Tokyo, Japan), h-caldesmon (h-CD; Agilent, Santa Clara, CA, USA), and α-SMA (1A4; Dako; Santa Clara, CA, USA) (Fig. 4F–H). In contrast, the sarcomatous component was positive for vimentin, desmin, h-caldesmon, and α-SMA and negative for all epithelial markers listed above

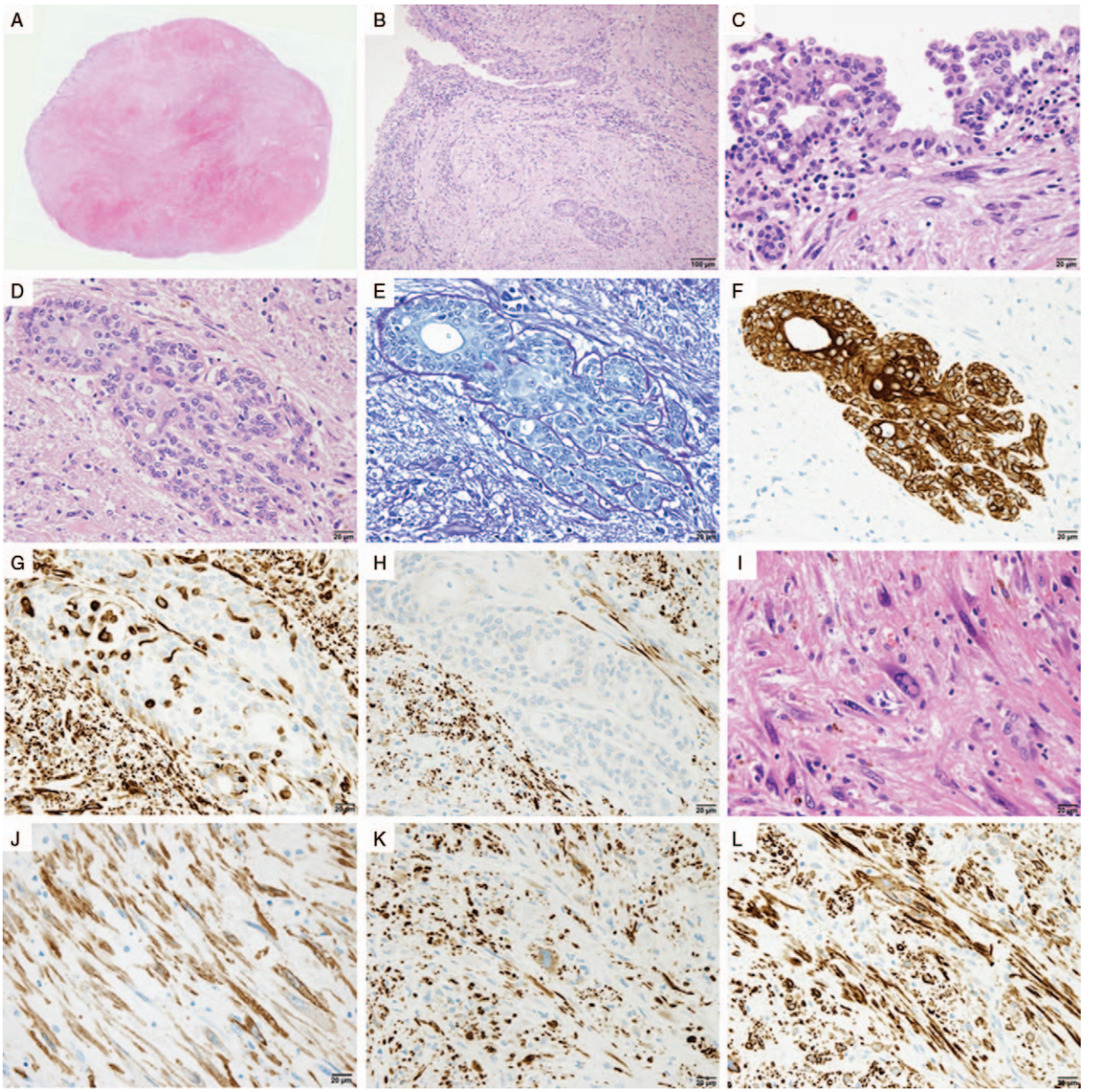

Figure 4. Photomicrographs of the tumor. (A) Low magnification of the tumor. (B) The surface of the tumor is covered with epithelial cells. Nests of epithelial component are observed inside the tumor (hematoxylin & eosin stain; the scale bar indicates 100 μm). (C) High magnification of the surface of the tumor showing the carcinomatous component. Atypical epithelial cells form an irregular glandular structure. Atypical spindle cells are also observed immediately beneath the epithelium (hematoxylin & eosin stain; the scale bar indicates 20 μm). (D) High magnification of nests of the carcinomatous component surrounded by the sarcomatous component (hematoxylin & eosin stain; the scale bar indicates 100 μm). (E) Alcian-blue & Periodic acid–Schiff double staining of carcinomatous nests. Positivity for alcian-blue staining indicates glandular differentiation. The basement membrane is partly obscured, suggesting invasive growth (the scale bar indicates 100 μm). (F) Immunostaining for broad-cytokeratin (AE1/AE3) showing positivity of the carcinomatous component and negativity of the surrounding sarcomatous component (the scale bar indicates 100 μm). (G, H) Immunostaining for vimentin and h-caldesmon showing negativity of the carcinomatous component and positivity of the sarcomatous component. Vimentin-positive cells inside the carcinomatous nest are infiltrating lymphocytes and histiocytes (the scale bar indicates 100 μm). (I) High magnification of the sarcomatous component. Nuclear inclusion body-like structures are observed in some of the atypical spindle cells (hematoxylin & eosin stain; the scale bar indicates 100 μm). (J–L) The sarcomatous component shows immunoreactivity for α-SMA, desmin, and h-caldesmon (the scale bar indicates 100 μm).

(Fig. 4J–L). Anaplastic lymphoma kinase 1 (ALK-1; Dako; Santa Clara, CA, USA) was negative through the tumor. Based on these findings, we diagnosed the tumor as carcinosarcoma.

The nephroureterectomy specimen showed incomplete ureteral duplication, hydronephrosis, and ureteral dilation (Fig. 3A). The tumor was likely to have originally located on the UPJ of the more severely dilated ureter. Microscopically, the ureteral mucosa of the more dilated mucosa showed severe inflammation with lymphoid follicle formation, while the other did not. However, we could not find any evidence of sarcoma, invasive carcinoma, carcinoma in situ or dysplastic epithelium in the background ureteral tissue.

Table 1

Immunohistochemical findings of the carcinosarcoma in the ureteropelvic junction.

Antibodies to	Carcinomatous component	Sarcomatous component
pancytokeratin (AE1/AE3)	+	−
low molecular weight cytokeratin (CAM5.2)	+	−
EMA	+	−
E-cadherin	+	−
uroplakin 2	+ (focal)	−
p63	+ (focal)	−
GATA3	+	−
vimentin	−	+
desmin	−	+
h-caldesmon	−	+
α-SMA	−	+
chromograninA	−	−
synaptophysin	−	−
CD56	−	−
myoD1	−	−
myogenin	−	−
p53 positive rate	20%	3%
Ki-67 labeling index	55%	15%

4. Discussion

Carcinosarcoma is a biphasic malignant tumor with carcinomatous and sarcomatous components. Sarcomatoid carcinoma is another term that is occasionally improperly used to refer to tumors exhibiting such features. Distinction between carcinosarcoma and sarcomatoid carcinoma has been a matter of controversy. The widely accepted criterion for distinguishing carcinosarcoma and sarcomatoid carcinoma is the presence or absence of epithelial characteristics in its sarcomatous component; carcinosarcoma lacks any immunohistochemical or ultrastructural evidence of epithelial differentiation in its sarcomatous component, whereas sarcomatoid carcinoma retains epithelial markers.[6,7,15,16] Based on this definition, the present case corresponds to carcinosarcoma. However, according to the latest World Health Organization classification of tumors of the urinary system, all urothelial carcinomas with sarcomatous components are collectively classified as sarcomatoid variants of urothelial carcinomas.[17]

The histogenesis of carcinosarcoma is hypothesized as follows: (1) collision tumor, which is developed through independent occurrences of carcinoma and sarcoma in close proximity that merge into one lesion; (2) composition tumor, which is developed through malignant transformation of both epithelial and mesenchymal components of the same tissue; (3) combination tumor, which is developed through divergent differentiation and malignant transformation of a single pluripotent stem cell; and (4) conversion tumor, which is developed through epithelial-to-mesenchymal transition of carcinoma.[18,19] In terms of clonality, the former 2 mechanisms are referred to as multiclonal theory, while the latter can be called monoclonal theory. The molecular evidence accumulated to date supports the monoclonal theory.[16,20–22] Additionally, many studies have revealed that carcinomatous and sarcomatous components showed significant overlap of genetic aberrations, suggesting the late occurrence of divergent differentiation during tumor development.[16,20,21] In other words, the sarcomatous component of carcinosarcoma is likely derived from the carcinomatous component in most cases. For the present case, however, the histogenesis is uncertain because we did not perform genetic analysis.

Malignant neoplasms accompanied by ureteral duplication are extremely rare; only 23 cases have been registered in English-language publications to date (Table 2).[23–43] Among them, urothelial carcinoma predominated, and only 2 cases were reported as sarcomatoid carcinoma with uncertainty of epithelial marker expression in the sarcomatous component.[35,40] Whether ureteral duplication is a risk factor for malignancy remains unclear. In contrast, horseshoe kidney, which is another common urinary tract malformation, is a risk factor for pelvic tumor.[12,44] The higher incidence of pelvic tumors in horseshoe kidneys is attributed to chronic irritability, such as urinary stasis, urinary tract infection, and stone formation.[12,44] Based on this speculation, it is reasonable to hypothesize that ureteral duplication is also a risk factor for malignancy because this anomaly is occasionally accompanied by urinary reflux and infection. Of note, 1 of the duplicated ureters of the present case, where the tumor is considered to have arisen, showed severe lymphocytic inflammation, which was evidently different from the other duplicate ureter.

The differential diagnosis of carcinosarcoma includes sarcomatoid carcinoma, carcinoma with reactive stromal proliferation, and carcinoma with a benign heterologous component. Sarcomatoid carcinoma can be differentiated by immunohistochemical studies based on the definition of carcinosarcoma/sarcomatoid carcinoma mentioned above. Carcinomas with reactive stromal proliferation and benign heterologous components can be differentiated by careful examination for malignant cytohistological features. If the sarcomatous component shows smooth muscle differentiation, as in the present case, inflammatory myofibroblastic tumor should be distinguished. A recent study showed that ALK-1 protein expression and ALK gene rearrangement were identified in approximately 60% of inflammatory myofibroblastic tumor cases in the urinary bladder, while sarcomatoid urothelial carcinoma was negative for ALK-1 expression and ALK rearrangement, indicating the utility of these markers in differential diagnosis.[45]

The prognosis of carcinosarcoma/sarcomatoid carcinoma of the upper urinary tract has not been systematically studied due to the paucity of cases. In the urinary bladder, to the best of our knowledge, 2 studies comparing the prognosis of carcinosarcoma and sarcomatoid carcinoma have been reported.[10,11] One study of 41 cases showed no significant difference in survival between carcinosarcoma and sarcomatoid carcinoma.[10] Conversely, another study of 301 cases concluded that the survival rate of sarcomatoid carcinoma is better than that of carcinosarcoma.[11] As noted in a recent review, the latter study has a limitation of not performing a central pathology review.[15] However, stratifying by T stage in survival analysis, which was not conducted in the former study, provides superiority of the latter study. Indeed, in the former study, there were more pT4 cases in the sarcomatoid carcinoma group than in the carcinosarcoma group, leaving the possibility that failure to show a significant difference in survival was due to selection bias. Given that carcinosarcoma and sarcomatoid carcinoma of the urinary tract may differ in clinical outcome, we believe that the distinction should be made between these 2 entities for further investigation.

In summary, carcinosarcoma of the upper urinary tract accompanied by ureteral duplication is extremely rare. Further studies are warranted to elucidate the association between

Table 2

Clinicopathological characteristics of 24 cases of malignant tumor accompanied by ureteral duplication.

Case	References [number]	Age (years)	Sex	Diagnosis	Tumor location	Duplication type	Symptoms	Treatment	pT stage	Metastasis	Local recurrence	Outcome	Follow-up period
1	Leadbetter et al. (1946) [23]	66	M	papillary carcinoma	right upper moiety pelvis	complete	painless hematuria	nephroureterectomy	not described	not described	not described	not described	not described
2	Tudor et al. (1986) [24]	56	F	urothelial (transitional cell) carcinoma	right lower moiety ureter (distal)	not described	painless hematuria	ureterectomy	pT2*	(–)	(–)	alive	2 months
3	Budd (1987) [25]	40	M	urothelial (transitional cell) carcinoma	right upper moiety pelvis	complete	painless hematuria	nephrectomy	not described	not described	not described	not described	not described
4	Sreenevasan et al. (1987) [26]	67	M	urothelial (transitional cell) carcinoma	right lower moiety ureter	incomplete	painless hematuria	nephroureterectomy	not described	(–)	(–)	alive	24 months
5	Gassner et al. (1989) [27]	47	M	urothelial (transitional cell) carcinoma with osseous metaplasia	left ureter	not described	flank discomfort, abdominal distension, dysuria	nephroureterectomy	not described	not described	not described	not described	not described
6	Gepi-Atte et al. (1991) [28]	74	M	urothelial (transitional cell) carcinoma	left upper moiety ureter (distal)	incomplete	painless hematuria	nephroureterectomy	pT2	not described	not described	not described	not described
7	Asase et al. (1992) [29]	66	M	urothelial (transitional cell) carcinoma	left lower moiety pelvis	incomplete	painless hematuria	nephroureterectomy	not described	not described	(–)	alive	3 months
8	Dudak et al. (1995) [30]	81	M	urothelial (transitional cell) carcinoma	left upper moiety ureter (distal)	complete	hematuria, flank discomfort	nephroureterectomy	pTa	not described	(–)	alive	7 months
9	Chung et al. (1996) [31]	42	F	leiomyosarcoma	left upper moiety pelvis	incomplete	none	nephrectomy	pT2a	not described	not described	not described	not described
10	Tan et al. (1996) [32]	62	M	urothelial (transitional cell) carcinoma	left ureter (middle) **	incomplete	painless hematuria, dysuria, abdominal pain, etc.	ureterectomy	pT1	(–)	(–)	alive	24 months
11	Zervas et al. (1997) [33]	38	M	urothelial (transitional cell) carcinoma ***	left ureter	not described	none	nephroureterectomy	pTis	not described	not described	not described	not described
12	Kawamura et al. (1998) [34]	67	F	urothelial (transitional cell) carcinoma	right ureter	incomplete	hematuria	nephroureterectomy chemotherapy	pT3	(–)	(–)	alive	6 months
13	Hisataki et al. (2001) [35]	43	F	sarcomatoid urothelial (transitional cell) carcinoma	left upper moiety pelvis	not described	flank pain	radical nephrectomy	not described	not described	(+)	dead	14 months
14	Li et al. (2002) [36]	74	M	urothelial (transitional cell) carcinoma	right upper moiety pelvis right lower moiety pelvis	incomplete	painless hematuria	nephroureterectomy	pT1	not described	(–)	alive	12 months
15	Chen et al. (2003) [37]	66	M	urothelial (transitional cell) carcinoma	right lower moiety pelvis	incomplete	painless hematuria	nephroureterectomy	not described	not described	(–)	alive	6 months
16	Chen et al. (2003) [37]	58	M	urothelial (transitional cell) carcinoma	right upper moiety pelvis left upper moiety pelvis left lower moiety pelvis	right complete left incomplete	painless hematuria	nephroureterectomy	not described	not described	(+)	dead	24 months
17	Chen et al. (2003) [37]	65	F	urothelial (transitional cell) carcinoma	left lower moiety ureter (distal)	incomplete	painless hematuria, nausea, vomitting, etc.	nephroureterectomy	not described	not described	(+)	alive	24 months
18	Unsal et al. (2003) [38]	68	F	urothelial (transitional cell) carcinoma	right upper moieter ureter (proximal)	complete	flank pain	nephroureterectomy	not described	(–)	not described	not described	not described
19	Boris et al. (2006) [39]	51	F	urothelial (transitional cell) carcinoma	right upper and lower moiety ureter (distal)	incomplete	hematuria	nephroureterectomy	pT1 or less*	not described	not described	not described	not described
20	Chen et al. (2011) [40]	77	M	sarcomatoid urothelial (transitional cell) carcinoma	left upper moiety pelvis	complete	abdominal pain, fever, anorexia	nephroureterectomy	pT3*	(–)	(–)	alive	not described
21	Kao et al. (2013) [41]	87	F	urothelial (transitional cell) carcinoma	left lower moiety ureter (proximal)	not described	hematuria, dysuria, abdominal fullness	radiotherapy	not described	not described	no surgery performed	dead	6 months
22	Ogawa et al. (2014) [42]	71	F	squamous cell carcinoma	left upper moiety pelvis	incomplete	hematuria, back pain	nephroureterectomy radiotherapy	pT4	not described	(–)	alive	6 months
23	Zhang et al. (2015) [43]	65	M	urothelial (transitional cell) carcinoma	right upper moiety pelvis	complete	hematuria, back pain	nephroureterectomy chemotherapy	not described	not described	not described	alive	not described
24	Present case	60	F	carcinosarcoma	right lower moiety ureteropelvic junction	incomplete	painless hematuria	nephroureterectomy	pT1	(–)	(–)	alive	21 months

* We determined the pT factors of these cases from pathological findings described in the articles based on the TNM Classification of Malignant Tumours, 8th edition.
** This patient had synchronous contralateral ureteral urothelial carcinoma without ureteral duplication.
*** Transitional cell carcinoma arose from a fibroepithelial polyp in this case.

ureteral duplication and malignancy as well as the clinicopathological correlation in carcinosarcoma/sarcomatoid carcinoma of the urinary tract.

Author contributions

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