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Case Report

Spontaneous carcinosarcoma originating from the renal pelvis in a rat

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Abstract: Carcinosarcoma is a rare neoplasm composed of malignant epithelial and stromal elements, and, for rats, carcinosarcomas in the kidney have not been reported. In a long-term study to gather background data, we encountered a spontaneous carcinosarcoma originating from the renal pelvis with metastasis to the lung. At necropsy, a mass was observed in the abdominal cavity, and white nodules were scattered in lung lobes. Microscopically, there was polypoid hyperplasia of the urothelium accompanied by hyperplasia of spindle stromal cells in the pelvis. The intra-abdominal tumor was composed of epithelial and stromal elements; in the lung, the tumor cells invaded along alveoli/bronchi and occasionally invaded the parenchyma from the blood vessels. Immunohistochemical and electron microscopic examinations revealed that the epithelial element consisted of transitional epithelial cells and that the stromal element consisted of lipoblasts. The tumor was diagnosed as a carcinosarcoma originating from the renal pelvis, and this is the first report of a carcinosarcoma originating from the renal pelvis in a rat. (DOI: 10.1293/tox.2016-0007; J Toxicol Pathol 2016; 29: 185–189)

Key words: carcinosarcoma, lung, metastasis, renal pelvis, spontaneous

Spontaneous renal tumors are sporadically found in untreated rodents of most strains with advancing age, and their histologic characteristics are comparable to those in humans[1]. In rats, reported renal tumors include the nephroblastoma, mesenchymal tumor, lipomatous tumor, and renal adenoma/carcinoma[2]. Unlike spontaneous urothelial tumors of the urinary bladder, spontaneous transitional cell carcinoma originating from the renal pelvis is very rare. Only 2 cases of transitional cell carcinoma metastasis from the renal pelvis have been reported[3, 4]. Furthermore, spontaneous carcinosarcomas in the kidney have not, to our knowledge, been reported. Carcinosarcomas are unusual neoplasms composed of malignant epithelial and stromal elements, and, in rats, the literature on carcinosarcomas is sparse[5, 6]. This report describes a case of spontaneous carcinosarcoma originating from the renal pelvis of an aged Sprague-Dawley (SD) rat with metastasis to the lung, which was composed of epithelial (transitional cell) and stromal (lipoblastic cell) elements.

The male SD (Crj: CD(SD)IGS) rat was a non-treated animal in a long-term study to gather background data. The animal showed poor physical condition accompanied by decreased body weight and food consumption from 72 weeks of age and was subsequently euthanized and necropsied at 74 weeks of age. At necropsy, a mass with a diameter of 3 to 4 mm and a thickened omentum was observed in the abdominal cavity. The mass surrounded the stomach and pancreas and was connected to the right kidney. There was a large quantity of reddish ascites. The cut surface of the intra-abdominal mass showed an area consisting of cysts of various sizes and white or dark red, solid areas (Fig. 1a). In the lung, a white nodule (10 × 6 × 4 mm) was found in the left lobe (Fig. 1b), and smaller white nodules (1 to 4 mm) were sporadically found in all lobes.

The intra-abdominal mass, pulmonary nodules, and kidneys were fixed in 10% neutral buffered formalin and were processed routinely for microscopic examination of paraffin-embedded sections stained with hematoxylin and eosin. The tissue sections were also stained immunohistochemically with mouse monoclonal anti-uroplakin III[7, 8] (Nichirei Bioscience, Tokyo, Japan), anti-vimentin (Dako Japan, Tokyo, Japan), anti-desmin antibodies (Dako Japan), and anti-proliferating cell nuclear antigen (PCNA) (Dako Japan) using an Envision system (Dako Japan) and visualized with diaminobenzidine tetrahydrochloride as the chromogen. The sections were counterstained with Mayer's hematoxylin. For electron microscopy, small pieces of formalin-fixed samples of the intra-abdominal mass were fixed in 2% phosphate-buffered glutaraldehyde, postfixed in 1%

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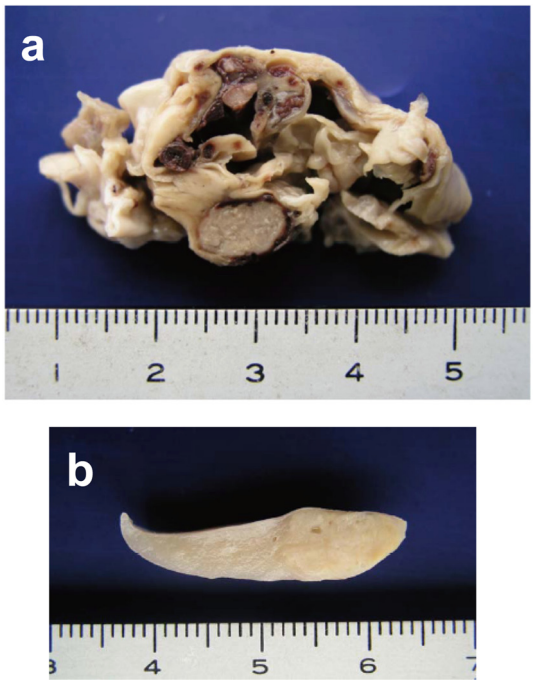

Fig. 1. Cut surfaces of the intra-abdominal mass and pulmonary nodules after fixation. The surface of the intra-abdominal mass showed an area consisting of cysts of various sizes and white or dark red solid areas (a). In the lung, a white nodule (10 × 6 × 4 mm) was found in the left lobe (b).

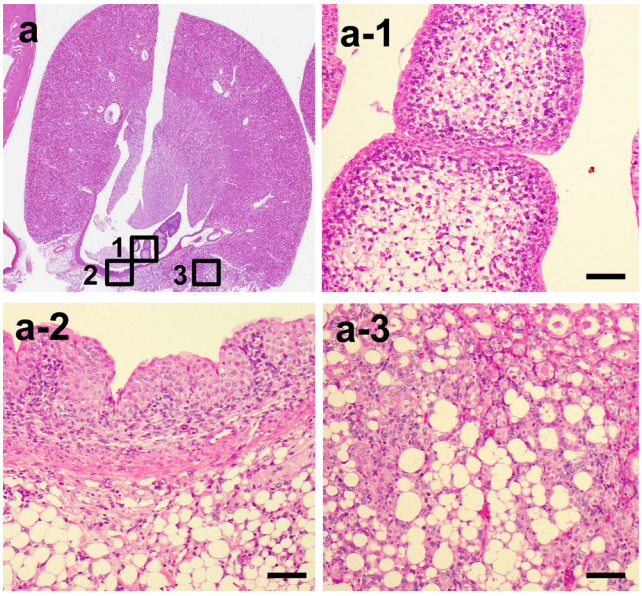

Fig. 2. Cross sections of the right kidney (a). Polypoid hyperplasia of urothelial cells accompanied by hyperplasia of spindle stromal cells was noted (a-1 and a-2). The stromal spindle cells were characterized by cytoplasmic vacuoles of various sizes and were prominent in the renal parenchyma (a-3). HE stain. Bars = 1 mm (a), 50 μm (a-1–3).

osmium tetroxide, and embedded in epoxy resin. Ultrathin sections were stained with uranyl acetate and lead stain solution (mixture of lead nitrate, lead acetate, and lead citrate) and examined with a JEM-100S electron microscope (JEOL Ltd., Tokyo, Japan).

Microscopically, there was polypoid hyperplasia of urothelial cells accompanied by hyperplasia of spindle stromal cells in the pelvis of the right kidney (Figs. 2a-1 and a-2). The stromal spindle cells were characterized by cytoplasmic vacuoles of various sizes and oval nuclei with scant chromatin indicative of lipoblast origin and were prominent in the renal parenchyma (Fig. 2a-3). The spindle stromal cells infiltrated into the renal medulla and capsule and were connected to the intra-abdominal tumor. The left kidney was histologically normal. The intra-abdominal tumor was primarily composed of the spindle stromal cells that were identical to those in the kidney (Fig. 3a). The spindle stromal cells formed large cysts, sometimes accompanied by an extensive necrotic area and hemorrhage (Fig. 3a). The tumor surface or inner wall of the large cysts was primarily covered with simple cuboidal mesothelial cells, and some areas were covered with a stratified epithelium morphologically identical to a transitional epithelium (Fig. 3b-1). Hyalinized glomeruli and degenerated renal tubules were infrequently present in the marginal area of the tumor mass (Figs. 3b-2 and b-3), which indicated that the origin was the renal pelvis, but not the ureter. In the lung, multiple foci of spindle stromal cells and transitional epithelial cells that were identical to the primary tumor were present. The foci consisted of multiple cysts covered with a transitional epithelium (Fig. 4a). The transitional epithelium invaded along the alveoli and bronchi and was accompanied by inflammation (Fig. 4a-1). Tumor emboli with spindle stromal cells and transitional epithelial cells were present in the blood vessel around the foci, and the tumor cells occasionally invaded the pulmonary parenchyma from the blood vessels (Fig. 4a-2). Thus our present case was composed of both epithelial and stromal elements with malignant characteristics, both of which exhibited distant metastasis.

The results of immunohistochemistry are summarized in Table 1. The transitional epithelium was positive for uroplakin III; the immunoreactivity was particularly strong in the superficial layer of the intra-abdominal tumor (Fig. 5a), pulmonary foci (Fig. 5b), and tumor emboli (Fig. 5c), while the spindle stromal cells were positive for vimentin in the intra-abdominal tumor (Fig. 6a) and pulmonary foci/tumor emboli (Fig. 6b). These tumor cells were negative for desmin; however, intact mesothelial cells covering the intra-abdominal tumor were positive. Most of the epithelial element and the spindle stromal cells were positive for PCNA, and a strong positive reaction was observed in the nuclei of basal cells of the transitional epithelium of the right renal pelvis and pulmonary foci.

Ultrastructurally, the spindle stromal cells in the intra-abdominal tumor had electron-lucent lipid droplets of various sizes without a limiting membrane in the cytoplasm, which indicated that they originated from lipoblasts (Fig. 7).

The possible differential diagnosis for the present tu-

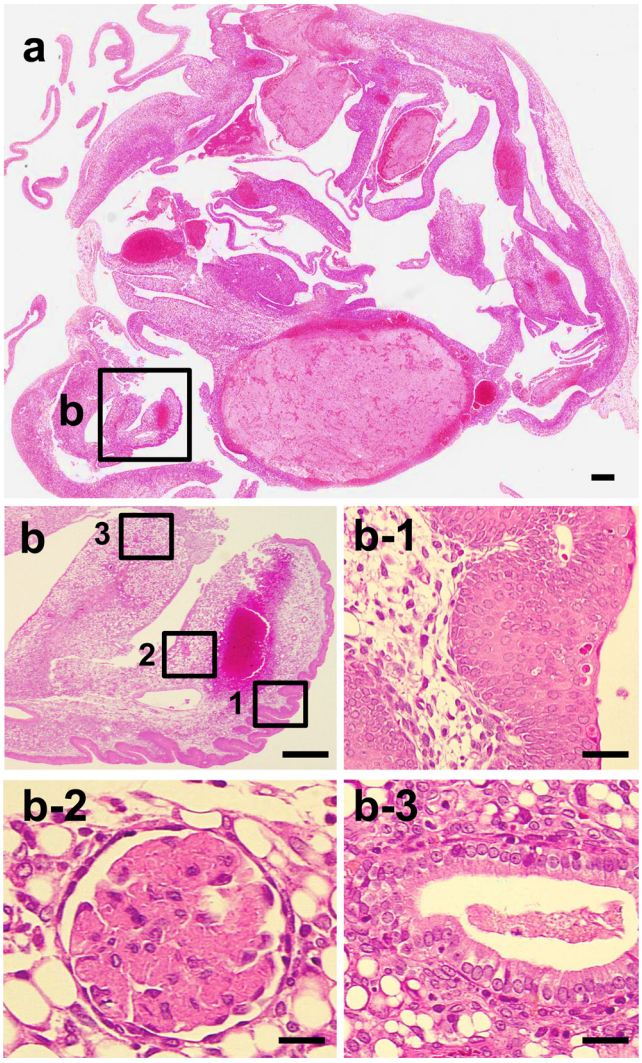

Fig. 3. Cross sections of the intra-abdominal mass (a). The spindle stromal cells proliferated, forming large cysts, and were sometimes accompanied by an extensive necrotic area and hemorrhage (b). The tumor surface or inner wall of the large cysts was primarily covered with simple cuboidal mesothelial cells, but some areas were covered with a stratified epithelium morphologically identical to a transitional epithelium (b-1). It was noteworthy that hyalinized glomeruli and degenerated renal tubules were present in the marginal area of the tumor mass (b-2 and b-3). Bars = 1 mm (a), 500 µm (b), 20 µm (b-1–3).

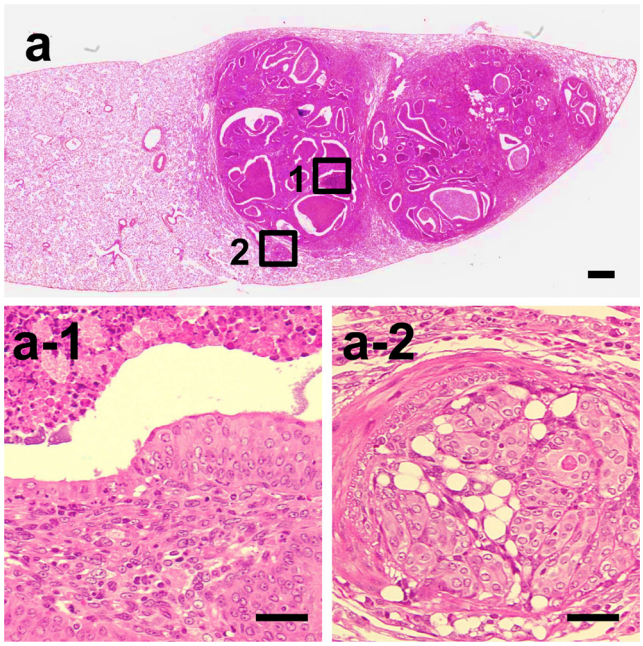

Fig. 4. Cross sections of the pulmonary nodules (a). Multiple foci of the tumor, which were composed of the spindle stromal cells and transitional epithelial cells and identical to the primary tumor, were present. The foci consisted of multiple cysts covered with a transitional epithelium. The transitional epithelium invaded along the alveoli and bronchi, sometimes merged with the bronchial ciliated epithelium, and was accompanied by inflammation (a-1). Tumor emboli with spindle stromal cells and transitional epithelial cells were present in the blood vessels around the foci (a-2). HE stain. Bars = 1 mm (a), 50 µm (a-1 and a-2).

Table 1. Results of Immunohistochemical Staining

	Intra-abdominal mass		Pulmonary nodule	
	Epithelial element	Stromal element	Epithelial element	Stromal element
Uroplakin III	+++	–	+++	–
Vimentin	–	+++	–	+++
Desmin	–	–	–	–
PCNA	+	++	+ ~ ++	++

Negative, –; weak, +; moderate, ++; strong, +++; NE, not examined.

mor includes nephroblastoma. Nephroblastoma arises from the metanephric blastema and has been reported to be typically a tumor of young rats[9]. Nephroblastoma in the rat is composed of epithelial elements surrounded by a nonneoplastic connective tissue stroma. In contrast, nephroblastoma in humans, commonly called Wilm's tumor, is composed of both neoplastic epithelial and connective tissue elements, and differentiation of the stroma into fibrous tissue, muscle, cartilage, bones, or neoplastic vascular structures has been reported[10]. In the present tumor, the pathognomonic feature of nephroblastoma, i.e., primitive basophilic blastemal cells, was not observed, and therefore, it was not considered to be a nephroblastoma. In addition, the histopathologic features of our case are different from those in the listed classification of rat renal tumors or other previously reported stromal tumors[9, 11].

In rodents, spontaneous carcinosarcomas originating from the kidney have not been reported, though there are a few reports on spontaneous urothelial tumors of the renal pelvis[4, 5, 12]. Carcinosarcoma originating from the urothelium is very rare in humans, and that originating from the upper urinary tracts is even less frequent[13, 14]. In humans,

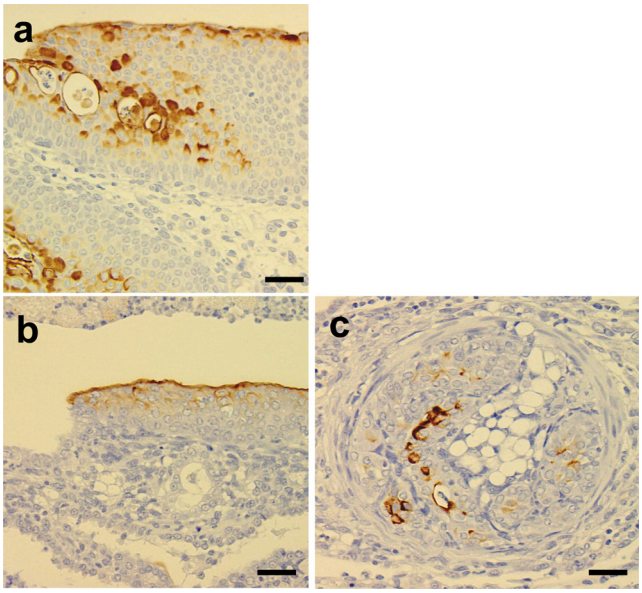

Fig. 5. Cross sections of the epithelial elements (transitional epithelium). Immunohistochemistry of uroplakin III in the epithelial element of the intra-abdominal mass (a) and pulmonary nodules (b and c). The transitional epithelium was positive for uroplakin III, and the immunoreactivity was strongly positive in the superficial layer of the intra-abdominal tumor (a), in pulmonary foci (b), and in tumor emboli (c). Bars = 50 µm.

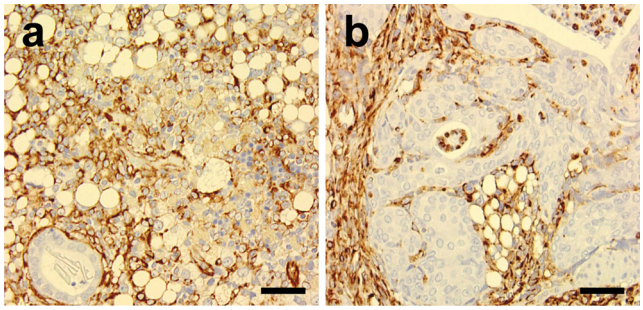

Fig. 6. Cross sections of the stromal elements (lipoblasts). Immunohistochemistry of vimentin in the stromal element of the intra-abdominal mass (a) and pulmonary nodules (b). The spindle stromal cells were positive in the intra-abdominal tumor (a), and pulmonary tumor emboli (b). Bars = 50 µm.

all the epithelial components were reported to be transitional cells, and the stromal components originating from the renal pelvis were diverse, i.e., malignant mesenchymoma, rhabdomyosarcoma, giant cell sarcoma, osteosarcoma, and chondrosarcoma[15–19]. In the present case, the stromal element was characterized by neoplastic stromal cells originating from lipoblasts, and this has not been reported in humans. Petersen[20] described 3 types of carcinosarcomas of the urinary tract: (i) collision tumors in which a carcinoma and a sarcoma arise in continuity and invade one another (ii) combination tumors in which carcinomatous and sarcomatous elements of the tumors arise from a totipotent cell, and (iii) composition tumors in which both malignant elements occur simultaneously in the same tissue. The latter two correspond to the true carcinosarcoma. The present case was categorized as a composition tumor according to the histological characteristics because of absence of undifferentiated blastemal tissue or continuity between the epithelial and stromal elements. The tumor emboli in the lung were considered to be blood-borne metastases from the intra-abdominal tumor with 2 distinct types of elements, and they also support this categorization.

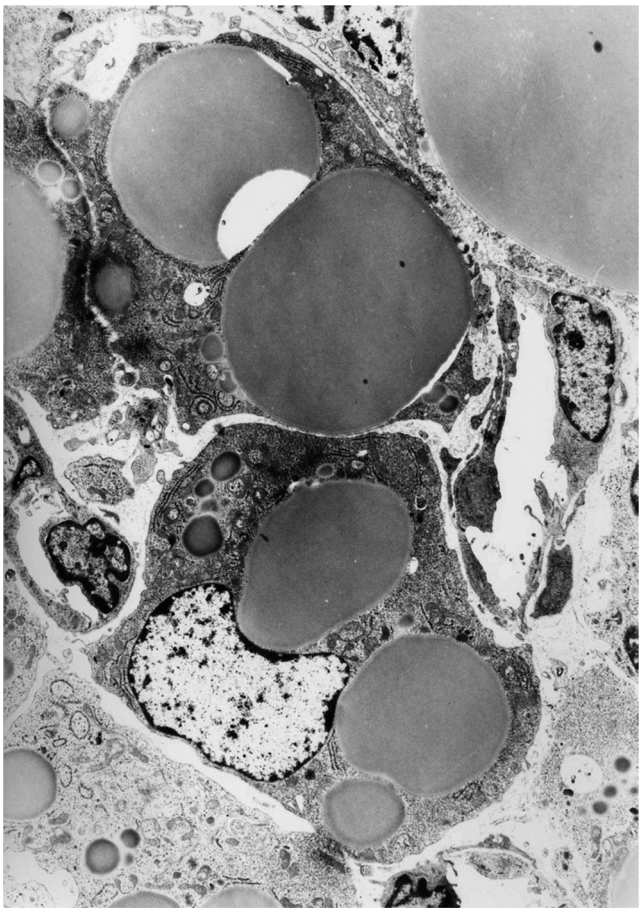

Fig. 7. Ultrastructure of the spindle stromal cells in the intra-abdominal tumor. Electron-lucent cytoplasmic lipid droplets of various sizes without a limiting membrane and an ovoid nucleus with scant chromatin were noted in the cytoplasm and indicated neoplastic stromal cells that originated from lipoblasts. ×3,500.

In conclusion, the tumor was diagnosed as a carcinosarcoma originating from the renal pelvis based on its histological and immunohistochemical features. To our knowledge, spontaneous carcinosarcomas in the kidney have not been reported in rats. This is the first report in an aged Sprague-Dawley rat, and carcinosarcoma originating from the renal pelvis should be included in the list of differential diagnoses of renal tumors in rats.

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References

1. Greaves P. 10. Urinary Tract. In: Histopathology of Preclinical Toxicity Studies: Interpretation and Relevance in Drug Safety Evaluation, 4th ed. Academic Press, Amsterdam. 537–614. 2012.
2. Montagomery CH, and Seely JC. Kidney. In: Pathology of the Fischer Rat. Boorman GA, Eustic SL, Elwell MR, Montgomery CA, Jr, and Mackenzie WF (eds). Academic Press, California. 127–153. 1990.
3. Maxie MG. The urinary system. In: Pathology of the Domestic Animals, Vol. 2. Jubb KVF, Kennedy PC, and Palmer N (eds). Academic Press, New York. 343–411. 1985.
4. Chandra M, Riley MGI, and Johnson DE. Incidence and pathology of spontaneous renal pelvis transitional cell carcinomas in rats. Toxicol Pathol. **19**: 287–289. 1991. [Medline] [CrossRef]
5. Burek JD. Chapter 4: Age-associated Pathology. In: Pathology of Aging Rats. CRC Press, Florida. 29–168. 1979.
6. Young S, and Hallowes RC. Tumors of the mammary gland. In: Pathology of Tumors in Laboratory Animals. Turusov VS (ed), Vol. I – Tumors of the Rat, Pt. 1. International Agency for Research on Cancer, Lyon, 31–74. 1973.
7. Moll R, Wu XR, Lin JH, and Sun TT. Uroplakins, specific membrane proteins of urothelial umbrella cells, as histological markers of metastatic transitional cell carcinomas. Am J Pathol. **147**: 1383–1397. 1995. [Medline]
8. Logani S, Oliva E, Amin MB, Folpe AL, Cohen C, and Young RH. Immunoprofile of ovarian tumors with putative transitional cell (urothelial) differentiation using novel urothelial markers: histogenetic and diagnostic implications. Am J Surg Pathol. **27**: 1434–1441. 2003. [Medline] [CrossRef]
9. Chandra M, Riley MGI, and Johnson DE. Spontaneous renal neoplasms in rats. J Appl Toxicol. **13**: 109–116. 1993. [Medline] [CrossRef]
10. Longaker MT, Adzick NS, Sadigh D, Hendin B, Stair SE, Duncan BW, Harrison MR, Spendlove R, and Stern R. Hyaluronic acid-stimulating activity in the pathophysiology of Wilms' tumors. J Natl Cancer Inst. **82**: 135–139. 1990. [Medline] [CrossRef]
11. Cardesa A, and Ribalta T. Nephroblastoma, kidney, rat. In: Monographs on Pathology of Laboratory Animals. Urinary System. Jones TC, Mohr U, and Hunt RD (eds). Springer-Verlag, New York, 71–80. 1986.
12. Kawai Y, Takada H, Yuasa H, Yamamura T, Inui T, and Okaniwa A. Spontaneous renal pelvic tumor in an aged rat. Nippon Juigaku Zasshi. **49**: 515–518. 1987. [Medline] [CrossRef]
13. Young RH. Carcinosarcoma of the urinary bladder. Cancer. **59**: 1333–1339. 1987. [Medline] [CrossRef]
14. Byard RW, Bell MEA, and Alkan MK. Primary carcinosarcoma: a rare cause of unilateral ureteral obstruction. J Urol. **137**: 732–733. 1987. [Medline]
15. Yoshida T, Ogawa T, Fujinaga T, and Kusuyama Y. [A case of carcinosarcoma originating from the renal pelvis]. Nippon Hinyokika Gakkai Zasshi. **81**: 1739–1742. 1990. [Medline]
16. Hou LT, and Willis RA. Renal carcino-sarcoma, true and false. J Pathol Bacteriol. **85**: 139–144. 1963. [Medline] [CrossRef]
17. Ridolfi RL, and Eggleston JC. Carcinosarcoma of the renal pelvis. J Urol. **119**: 569–572. 1978. [Medline]
18. Tarry WF, Morabito RA, and Belis JA. Carcinosarcoma of the renal pelvis with extension into the renal vein and inferior vena cava. J Urol. **128**: 582–585. 1982. [Medline]
19. Chen KTK, Workman RD, Flam MS, and DeKlotz RJ. Carcinosarcoma of renal pelvis. Urology. **22**: 429–431. 1983. [Medline] [CrossRef]
20. Petersen RO. Carcinosarcoma. In: Urologic Pathology. Petersen RO (eds). JB Lippincott, Philadelphia. 130–133. 1986.