Multiple carcinosarcomas of the kidney: A case report and review of the literature

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Abstract. Carcinosarcomas are biphasic tumors comprising epithelial and mesenchymal components. Primary carcinosarcoma of the kidney is extremely uncommon and accounts for <1% of all malignant renal tumors. Primary carcinosarcoma of the kidney generally occurs after the age of 60 and the majority of the patients are men. This is the case report of a 56-year-old male patient who presented with left flank pain. Ultrasonography and computed tomography (CT) revealed ureterohydronephrosis and a left distal ureteral stone (25 mm). Renal scan with diethylenetriamine pentaacetate and dimercaptosuccinic acid revealed a non-functional kidney and a left nephroureterectomy was performed. The pathological examination of the surgical specimen revealed high-grade multiple carcinosarcomas according to the Union for International Cancer Control and cancer staging according to the tumor-node-metastasis classification determined the disease as stage T3aN0M0. At 6 months, the patient was administered systemic adjuvant chemotherapy (CTx) due to widespread lung and liver metastases on ^{18}F-fluorodeoxyglucose positron-emission tomography/CT. However, no response was achieved with systemic CTx. The precise histogenesis of this type of cancer has not been determined. Carcinosarcoma of the kidney is a biphasic tumor and its biphasic nature must be confirmed using immunohistochemical methods during pathological diagnosis. The mesenchymal components of sarcomatoid carcinomas must be verified by pathological examination. Metaplastic changes may have malignant potential but should not be considered as malignant lesions. The most significant histopathological parameter that supports the diagnosis of sarcomatoid carcinoma is the identification of transitional zones between the epithelial and mesenchymal cells. Carcinosarcoma is characterized by aggressive malignant potential and a poor prognosis. An effective curative method has not yet been established, with the exception of radical surgery. It is therefore recommended to perform efficient surgical excision with adequate surgical margins.

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Introduction

The case reports on carcinosarcoma of the kidney are extremely rare in the literature. Sarcomatoid kidney carcinoma was first described by Farrow *et al* (1) in 1968. However, carcinosarcoma of the urinary tract was first described by Robson (2) in 1935. Although this type of tumor accounts for <1% of all malignant renal tumors, it requires strict follow-up upon establishing the diagnosis due to its aggressive nature and high metastatic potential. The presence of the sarcomatoid component is an indication of an aggressive tumor nature (3). Carcinosarcoma of the kidney is a biphasic tumor and the biphasic nature of the tumor must be confirmed using immunohistochemical methods while establishing the pathological diagnosis (4). Tumor location in the renal pelvis and calyceal epithelial components together with mesenchymal malignant components have been considered to promote early metastasis (3).

Case report

Clinical characteristics. A 56-year-old male patient presented with left flank pain persisting over the previous 6 months. The patient's history included diabetes mellitus and heavy smoking. The liver function tests were normal. The blood biochemistry results were as follows: Glucose, 153 mg/dl; creatinine, 1.5 mg/dl; urea, 56 mg/dl; white blood cell count, 7.11x10^3/μl; hemoglobin, 12.3 g/dl; platelet count, 308,000 mm^3; sodium, 133 mmol/l; potassium, 4.9 mmol/l; chloride, 103 mEq/l; calcium, 8.6 mg/dl; and erythrocyte sedimentation rate, 42 mm/h. On physical examination, there was tenderness on palpation in the left lumbar region. Ultrasonography revealed left-sided grade IV hydronephrosis and the computed tomography (CT) revealed left ureterohydronephrosis and a urinary stone in the left distal ureter measuring 25 mm in diameter. Renal scan with dimercaptosuccinic acid and diethylenetriamine pentaacetate revealed a non-functional left kidney and the patient underwent a nephroureterectomy.

Immunohistopathological characteristics. On macroscopic examination, the nephroureterectomy specimen included the left kidney, measuring 18x13x8 mm, a ureteral segment

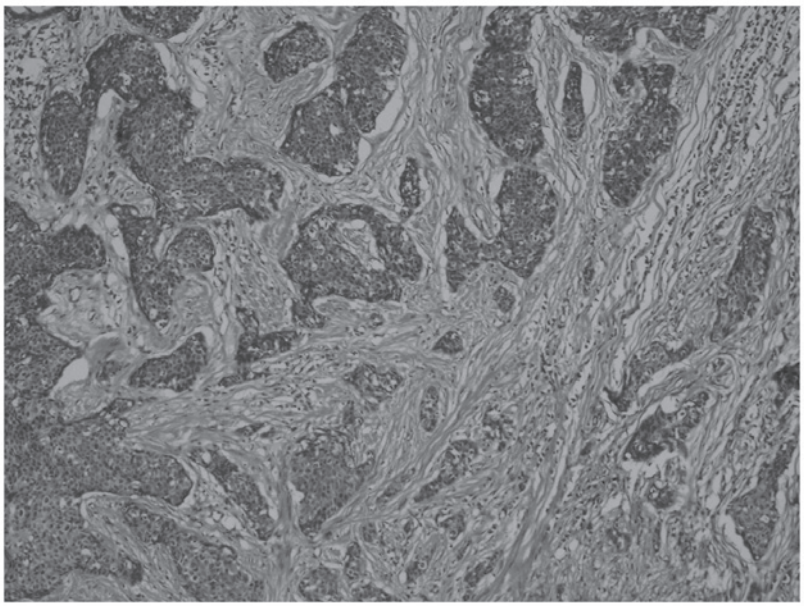

Figure 1. Carcinomatous cells embedded in a desmoplastic stroma. Hematoxylin and eosin staining (magnification, x40).

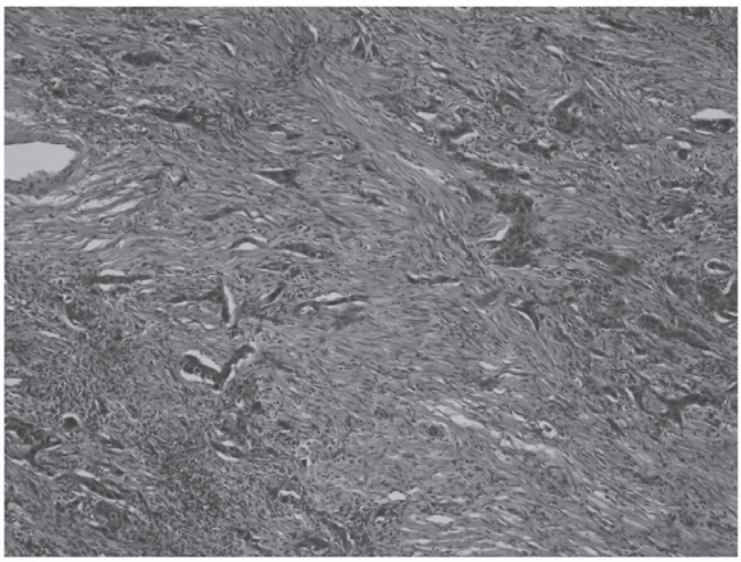

Figure 2. Marked pleomorphism with atypia, spindle cells and sarcomatous areas. Hematoxylin and eosin staining (magnification, x40).

190 mm in length and a ureteral calculus measuring 25 mm in diameter. The thickness of the renal cortical parenchyma was reduced to 1 mm. Three nodular lesions with irregular margins, brown to dark yellow in color were identified in the kidney, with the largest of the lesions measuring 30 mm in diameter. The total diameter of the nodular lesions was 70 mm. The microscopic examination of the lesions revealed tumor cells with fusiform nuclei and a pink cytoplasm, exhibiting diffuse pleomorphism and areas of necrosis. The mitotic count was 19-20/10 high-power fields. Islands of carcinomatous cells were identified, embedded in a desmoplastic stroma [hematoxylin and eosin (H&E) staining; magnification, x40; Fig. 1]. Sarcomatous areas, composed of pleomorphic fusiform cells with marked atypia were also identified (Fig. 2) (H&E staining, magnification, x40).

On immunohistochemical examination, the tumor cells were pan-cytokeratin$^+$, DKA$^+$, desmin$^+$, vimentin$^+$, CD117$^-$, CD34$^-$ and S-100$^-$ (Figs. 3 and 4). The Ki-67 proliferation index was 70%. Sarcomatous components were identified, together with carcinomatous components and transitional zones between the two. The transitional zones between sarcomatous and carcinomatous areas are demonstrated in Figs. 3 and 4, using pan-cytokeratin and vimentin immunostaining, respectively.

Staging, treatment and outcome. According to Union for International Cancer Control and the tumour-node-metastasis staging system of the European Association of Urology, the case was diagnosed as high-grade, stage T3aN0M0 cystic carcinosarcoma of the kidney (5). On conventional cystoscopy, there was no concomitant bladder tumor. Distant metastasis was not observed at the time of the diagnosis and during nephroureretectomy. However, widespread lung and liver metastases were identified on ^{18}F-fluorodeoxyglucose positron-emission tomography/CT at 6 months follow-up and systemic adjuvant

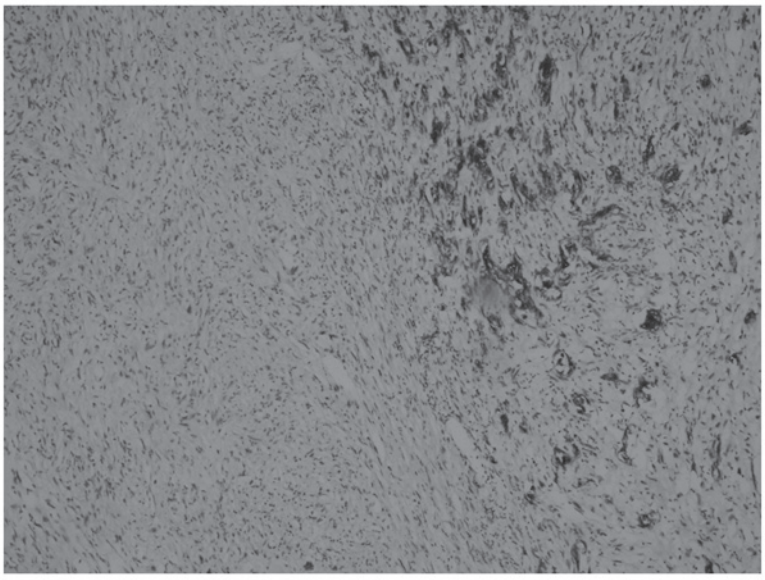

Figure 3. Immunohistochemical staining with pan-cytokeratin showing cytokeratin-negative sarcomatous areas on the left and cytokeratin-positive carcinomatous areas on the right (magnification, x40).

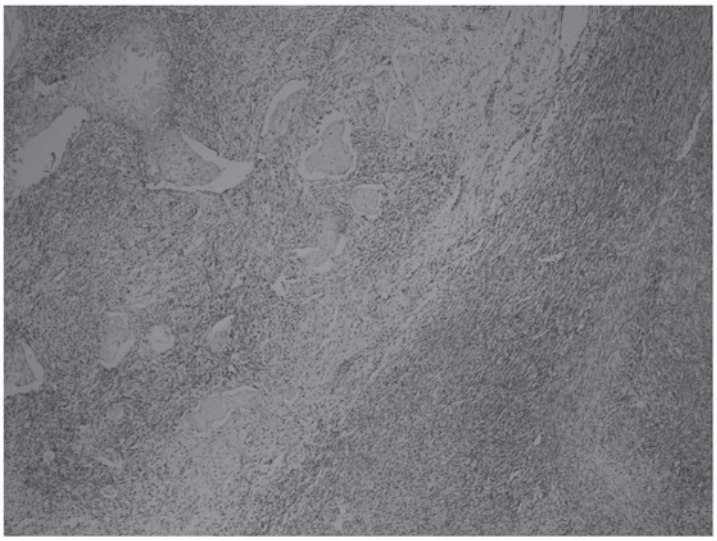

Figure 4. Immunohistochemical straining with vimentin showing vimentin-negative carcinomatous areas on the left and vimentin-positive sarcomatous areas on the right (magnification, x40).

chemotherapy (CTx) was administered. However, there was no response to CTx. The patient was succumbed to the disease in the first year of follow-up.

Ethics statement and informed consent. All the procedures were in accordance with the ethical standards of the responsible Committee on Human Experimentation and with the Helsinki Declaration of 1975, as revised in 2000. Written informed consent was obtained from the patient.

Discussion

According to the World Health Organization classification of urothelial cancers in 2014, it is recommended to use the term 'sarcomatoid carcinoma' for all biphasic malignant tumors in which epithelial and mesenchymal differentiation is confirmed using morphological and/or immunohistochemical criteria (6). However, both definitions were used in this study. Sarcomatoid carcinomas may occur in any location in the urinary tract. Sarcomatoid carcinoma of the bladder is the most common occurrence reported in the literature. Sarcomatoid carcinoma of the kidney is less common, but it is an aggressive tumor with a high metastatic potential. Sarcomatoid carcinoma of the kidney most commonly occurs at ages ≥60 years and the majority of the patients are men. Sarcomatoid carcinomas are solitary tumors and rarely occur in multiple locations (7). Contrary to the information reported in the literature, our case presented with mass lesions in 3 different locations in a cystic hydronephrotic kidney.

There are also other case reports on the multifocal occurrence of these lesions. Ishumura *et al* (8) reported a case with multiple carcinosarcomatous lesions located concurrently in

the kidney and in different locations in the ipsilateral ureter. Sarcomas occur as solitary tumors; however, the identification of tumor lesions with similar histopathological characteristics in different locations of the kidney in the present case suggests that they may be affected by similar carcinogenic factors. The underlying chronic urinary tract obstruction secondary to ureteral lithiasis may have triggered the development of the disease in multiple locations independently from one another. The factors triggering the development of this disease have not yet been clearly determined. Sarcomatoid carcinomas are biphasic tumors with carcinomatous and sarcomatous components that are considered to arise from primitive pluripotent stem cells (9). However, the precise histogenesis of this type of cancer has not been fully elucidated (10). Wang *et al* (11) identified duplications of chromosomes 3, 7 and 17 and deletion of chromosome 9p21 as the common genetic alterations among sarcomatoid carcinomas of the upper urinary tract.

The biphasic components of the primary carcinosarcoma of the kidney include epithelial and mesenchymal components. The most common epithelial components are urothelial carcinoma, carcinoma *in situ*, adenocarcinoma, squamous cell carcinoma and small-cell carcinoma. The most common mesenchymal component is leiomyosarcoma and less common components include rhabdomyosarcoma, liposarcoma, osteosarcoma, angiosarcoma, fibrosarcoma, chondrosarcoma, malignant Schwannoma and Ewing's sarcoma (12). The present case was diagnosed with high-grade transitional cell carcinoma together with high-grade leiomyosarcoma. The mesenchymal components of sarcomatoid carcinomas must be confirmed by pathological examination. Osseous and chondroid metaplasia and carcinomas with pseudosarcomatous stroma must be excluded, as metaplastic changes may have malignant potential, but they should not be considered as malignant lesions. One of the most significant histopathological parameters that supports the diagnosis of sarcomatoid carcinoma is the identification of transitional zones between epithelial and mesenchymal cells (10).

The epithelial and mesenchymal components must be distinguished using immunohistochemical methods. The presence of diffuse and marked mitotic activity and atypical mitoses support the diagnosis of sarcomatoid carcinoma (12). Carcinosarcomas are malignant and highly aggressive tumors with a high metastatic potential. Radical nephrectomy is the primary treatment method for renal carcinosarcoma. No beneficial effect of adjuvant radiotherapy and CTx has been demonstrated thus far (9). We did not achieve any response to adjuvant CTx in the present case. The most commonly used chemotherapeutic agents include cisplatin, dacarbazine, docetaxel, gemcitabine, methotrexate, oxaliplatin, doxorubicin, paclitaxel, vincristine and vinorelbine. However, no treatment protocol has been established for adjuvant CTx.

Carcinosarcomas may be asymptomatic, but they may also present as palpable lumbar or abdominal masses, accompanied by lumbar or abdominal pain and hematuria. The patients may also exhibit systemic symptoms, including anorexia, weight loss, malaise, fatigue, fever, night sweats or cough (13).

The etiology of sarcomas remains unknown and there is no sufficient data on their biological behavior. In the literature, there are reports of cases who sustained spontaneous intraperitoneal rupture and life-threatening hemorrhage due to the aggressive nature of carcinosarcomas (14). This type of biphasic tumor is associated with poor prognosis and such tumors are devoid of natural barriers due to the mesenchymal tissue arising from the sarcomatoid component, whereas the tumors typically carry a pseudocapsule. These tumors have high metastatic potential and multifocal occurrence is an indicator of poor prognosis (15), with a 5-year survival rate of <10% in T3 tumors (16). In the present case, multifocal involvement and with advanced stage reduced the life expectancy of the patient.

In conclusion, primary carcinosarcoma of the kidney is a rare tumor with aggressive bilogical behavior and a high metastatic potential. The patients should be closely monitored due to the unknown or unpredictable biological behavior of this tumor. The scarcity of the described cases in the literature does not allow for efficient histopathological classification and staging, further complicating the selection of the appropriate treatment modality with respect to disease stage. Our basic knowledge on carcinosarcomas of the kidney dictates the need for a multidisciplinary approach, including radical surgical excision, radiotherapy and adjuvant CTx.

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