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A case report of primary osteosarcoma originating from kidney

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Abstract

Rationale: Primary osteosarcoma of the kidney is a very rare subtype of renal neoplasms. There are only 27 cases reported in the literature since 1936. In addition, it has a high risk of metastasis and very low survival rate.

Patient's concerns: In this report, we present a case of unique large osteosarcoma originated from the left kidney (21 cm × 18 cm × 11 cm) with lung metastasis. A 48-year-old female patient presented with intermittent abdominal distension and gross hematuria.

Diagnoses: A computed tomography scan of the abdomen confirmed a large solid, partly calcified mass in the left retroperitoneum, with lung metastasis (IV stage according to AJCC). The radical nephrectomy was performed. The postoperation immunohistochemical analysis supporting the diagnosis of osteosarcoma.

Interventions: The patient received chemotherapy with ifosfamide, cisplatinum, pirarubicin and then target therapy with anlotinib (12 mg per day, per os; days 1–14; 21 days per cycle) after surgery.

Outcomes: The patient was followed up for 26 months, with no postoperative complications, no tumor recurrence, and no progress in pulmonary metastasis.

Lessons: The case reported here is a unique large osteosarcoma originated from the kidney (21 cm × 18 cm × 11 cm) at an advanced stage (IV). However, the patient's condition was controlled for at least 26 months after surgical resection and postoperative chemotherapy, which had never been reported in the literature before. Additionally, 3 mutated genes were found in the tissue by genetic testing, which we suspect that is the reason why this patient is sensitive to chemotherapy and thus has longer survival.

Abbreviations: FDG = ^{18}F-fluorodeoxyglucose, HE = hematoxylin-eosin, PET-CT =Positron emission tomography–computed tomography, RCC = renal cell carcinoma, VIM = vimentin.

Keywords: fluorodeoxyglucose, oncogene, renal sarcoma, soft tissue sarcoma, urologic neoplasms

1. Introduction

Extraskeletal osteosarcoma is a very rare disease and accounts for approximately 1% of all soft tissue sarcomas and <4% of all osteosarcomas.[1] A few extraskeletal osteogenic sarcomas have been reported in the literature, but the involvement of the kidney was rare. The incidence of primary osteosarcoma in the kidney is extremely rare. Only 27 cases have been reported in the literature since 1936. Given the aggressive nature of these tumors, the overall prognosis rate is very poor. The rate of local recurrence, as well as distant metastasis, is approximately 86% (24/28), which is very high, with approximately 32% (9/28) of patients presenting with metastasis when diagnosed (including our case).[1–24] Here, we present a case of primary osteosarcoma of the kidney and review its clinical presentation, diagnosis, and treatment options.

2. Case reports

A 48-year-old female patient presented with a 6-month history of intermittent abdominal distension and 2 months of gross hematuria for the first time in July 2016. Abdominal physical examination revealed a left mass in the hypochondrium and iliac fossa. The rest of the physical examination showed no significant abnormalities.

Routine urine tests revealed an elevated number of red blood cells displaying homogeneity. Routine blood examination indicated anemia. Other biochemical profiles were within normal limits, except for a markedly elevated serum alkaline phosphatase levels at 1800 IU/L. Urinary cytology did not detect any malignant cells.

A computed tomography (CT) scan of the abdomen confirmed a large solid, partly calcified mass in the left retroperitoneum with the lumbar muscle infiltrated and closely related to the abdominal aorta (Fig. 1A and B). The maximum diameter was 18 cm, and there were patchy low-density lesions and calcification foci, with no enlarged lymph nodes. The source of the mass was considered to be the kidney. The nuclear bone

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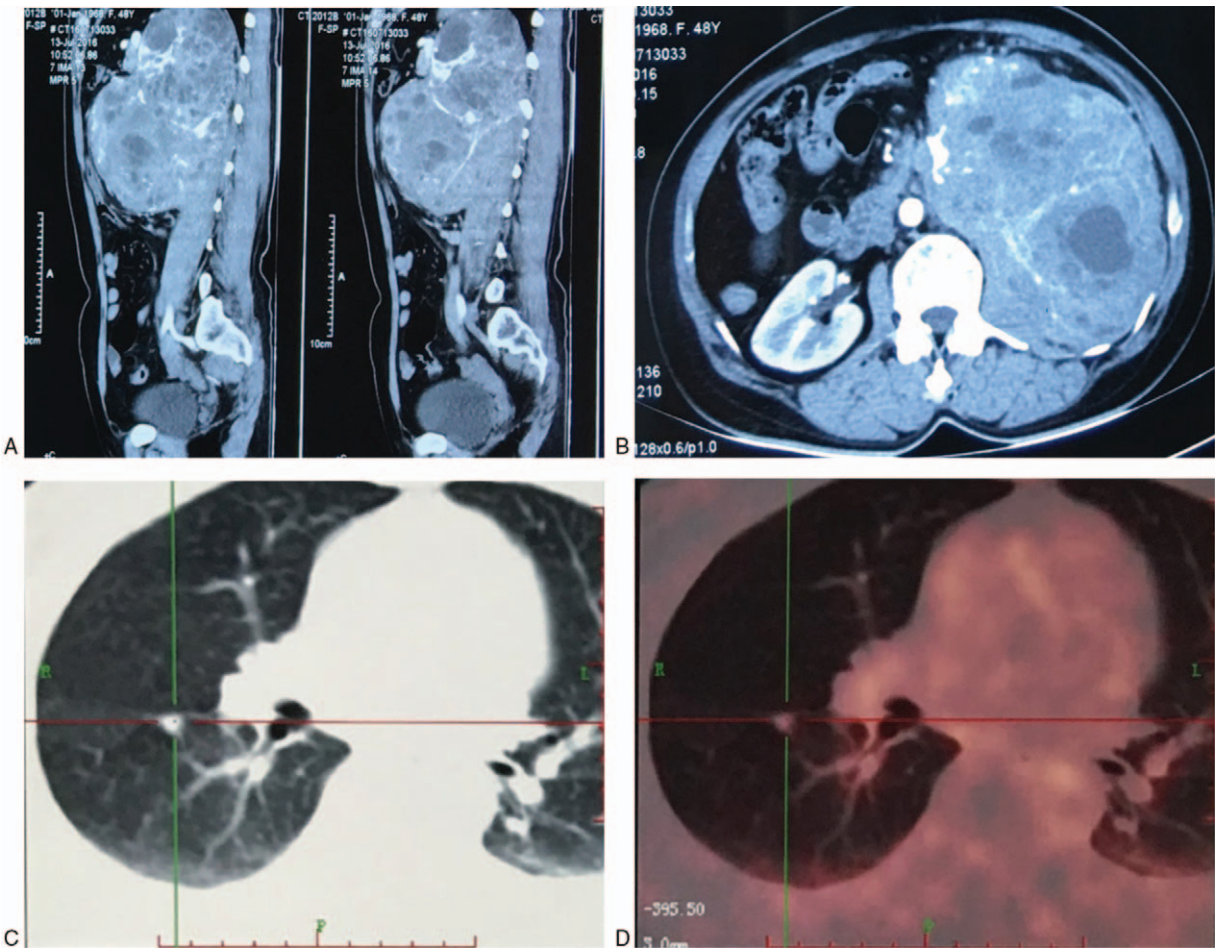

Figure 1. (A and B) Axial and sagittal computer tomography scans showing a large tumor with calcifications in the retroperitoneum. (C and D) Positron emission tomography–computed tomography scans showing focal activity in the lung, concern for metastatic disease (at the intersection).

scan was normal. ^{18}F-fluorodeoxyglucose Positron emission tomography–computed tomography (PET-CT) for the whole body shows that the glucose metabolism is slightly higher in the right lower lung and a metastatic tumor is considered to be present (Fig. 1C and D). From the abovementioned information, we preoperatively diagnosed this mass to be a large renal cell carcinoma featuring calcifications with lung metastasis. This patient is at stage IV according to the AJCC cancer staging manual.[2,5] After communicating with the patient's family, we made an MDT (multiple disciplinary team) treatment plan that included the Department of Urology, Vascular Surgery, Oncology and CT center. The details of the plan are as follows: the radical nephrectomy will be performed by the Department of Urology and Vascular surgery and the patient will receive chemotherapy or radiotherapy after surgery according to the results of the pathology examination.

After gross examination, the kidney revealed a 21-cm 18-cm × 11-cm large tumor replacing the kidney (Fig. 2A). The surface cut showed central yellow-brownish, rock-hard masses with areas of hemorrhage and necrosis (Fig. 2B). The tumor specimens were subjected to pathological examination. Microscopic examination of the hematoxylin–eosin stain demonstrated a diffuse arrangement of different sizes of spindle cell proliferation with interspersed osteoid of variable calcification (Fig. 3A and B). No sections had malignant epithelial elements. The resected ureteric margin failed to find any evidence of a tumor. The immunohistochemical analysis was positive for vimentin (VIM), SAM, Ki67, and CD10 and negative for renal clear cell carcinoma (RCC) and CK, supporting the diagnosis of osteosarcoma. Genetic tests showed 3 variants (MSH6, FANCF, and ERCC4) identified among 124 genes tested.

The patient had an uneventful postoperative recovery and was transferred to the Department of Oncology to receive chemotherapy. While in the Oncology Department, the patient received 5 rounds of chemotherapy with ifosfamide, cisplatinum, and pirarubicinand and then received target therapy with anlotinib (12 mg per day, per os; days 1–14; 21 days per cycle) until currently. The patient exhibited a good prognosis at 26 months of follow-up, with no evidence of local recurrence and no worsening of the lesion in the lung. The patient provided informed consent for the publication of her clinical and radiological data.

3. Discussion

The clinicopathological features of 28 cases including our case are summarized in Table 1. The data suggest that the male-to-female ratio is 4:3; the age ranges from 29 to 82 (median age = 59); the left-to-right ratio is 17:10, with 1 unclear case. Flank pain and hematuria seem to be the most common complaint, followed by weight loss and some symptoms of the digestive tract. This is

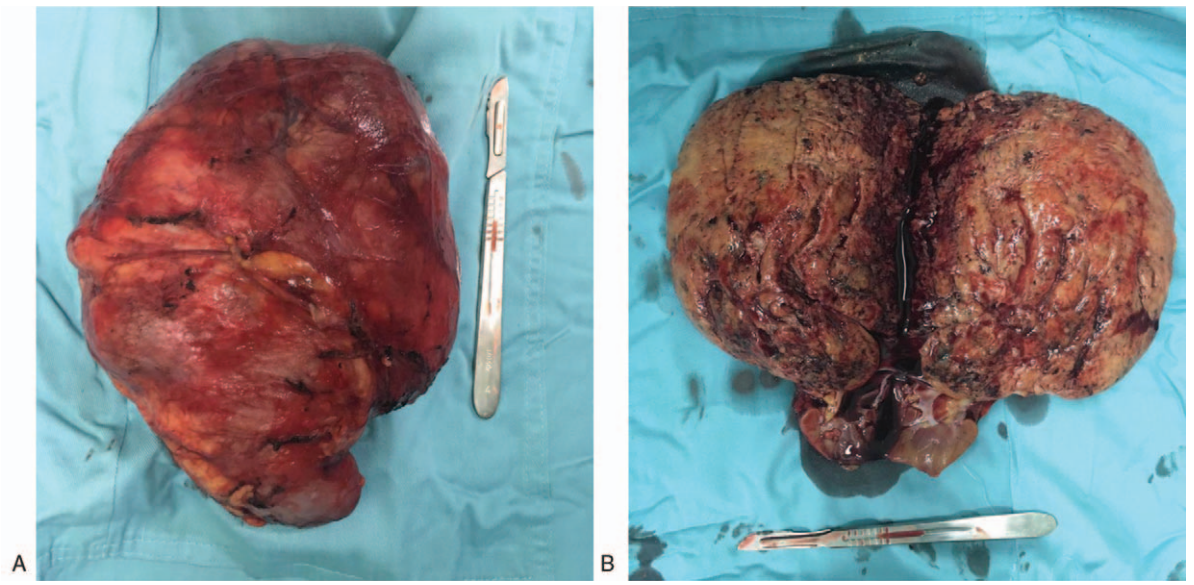

Figure 2. (A) Gross features of the large tumor (21 cm × 18 cm × 11 cm) replacing the kidney entirely. (B) The hemisection shows yellow-brownish, rock-hard masses with areas of hemorrhage and necrosis.

different from RCC, in which flank pain is not the usual dominant complaint.[29]

Osteosarcoma originating in the kidney is aggressively growing and extremely fatal; it easily infiltrates contiguous structures and metastasizes. It is most commonly seen in the adrenal gland, spleen, liver, and lungs. Approximately 24 of the 28 (86%) patients present distant metastasis or the infiltration of contiguous organs. The average overall survival (OS) is approximately 10 months; this is likely because of their advanced stage when they are presented. Biochemical blood test results are often normal except for the serum level of alkaline phosphatase, which may help to diagnose or monitor recurrence. The "sunburst" appearance is relatively characteristic on a CT scan.

Given that RCC is the most common renal tumor diagnosed, it is crucial to distinguish the ossification of RCC from primary renal osteosarcoma. First, metaplastic bone formation in RCC is very rare; second, the absence of carcinoma is vital in diagnosing primary osteogenic sarcoma instead of RCC with ossification; third, they have different histologic origins, in which RCC comes from the epithelium while osteosarcoma originates in the mesenchyme. Immunohistochemistry helps to identify the histologic origin (such as positive for VIM, S100, SMA, and Ki67; negative for CK, RCC, and EMA).

The exact histogenesis of osteosarcoma of the kidney remains unclear. According to Virchow's theory, first proposed in 1884 and still prevailing today, in certain circumstances, there is a metaplastic transformation of the connective tissue to embryonic mesenchyme with the ability to differentiate into osteoblasts and bones.[30] The spindle cell sarcomatous status in the osteogenic areas, as noted in our case and most in the literature, tends to support this concept.

We performed genetic testing on this patient after surgery including 124 common tumor-associated genes and found that 3 genes (MSH6, FANCF, and ERCC4) had variations. These variants are expected to result in the loss of functions of the protein products from the genes. The gene-related tumor spectrum of MSH6 includes colorectal, endometrial, ovarian, and other cancers.[31] Jentzsch et al reported that significantly

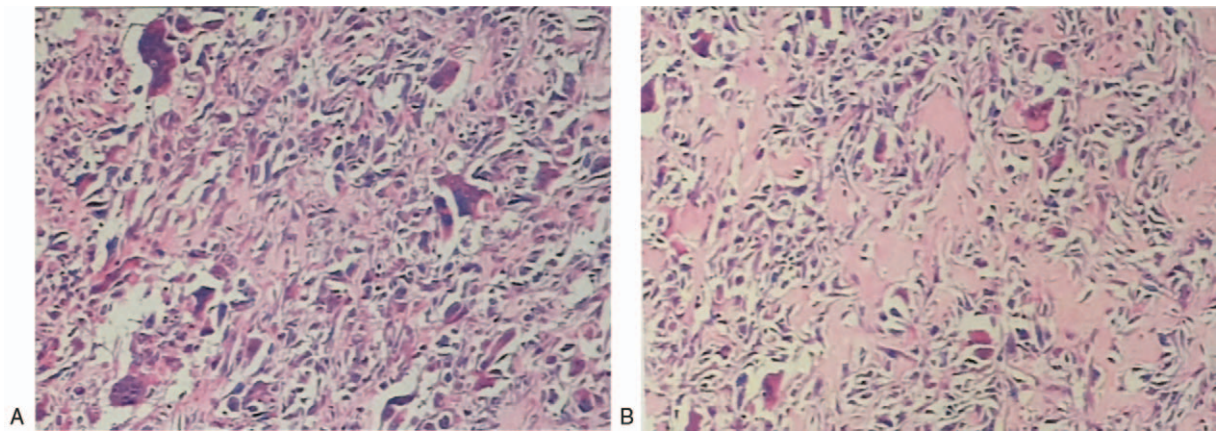

Figure 3. (A and B) Hematoxylin–eosin staining (100×) shows focal necrosis, spindle cells, and focal areas containing osteoid.

Table 1

Overview of the cases reported in the literature.

Reference	Age/gender/ side	Presenting symptoms	Risk factors/ pertinent history	Treatment	Outcome	Tumor size	Metastases	AJCC stage	Biochemical profile
Haining[2] (1936)	76/M/L	Hematuria	None known	None	Not mentioned	Not mentioned	Liver, bowel, and right kidney	IV	
Hamer and Wishard[3] (1948)	76/M/R	Hematuria	None known	Radiotherapy	1 month	Not mentioned	Lungs	IV	
Hudson[4] (1956)	52/F/L	Flank pain and hematuria	None known	Radical nephrectomy	Died 4 months after surgery	Not mentioned	Transverse colon	?	
Soto et al[5] (1965)	82/F/L	Flank pain, gross hematuria, and loss weight	None known	Radical nephrectomy	Died 82 days after surgery	15 cm × 14 cm × 9 cm	Lungs, liver, and omentum	IV	
Johnson et al[6] (1970)	59/F/R	Flank pain, nausea, and vomiting	None known	Radical nephrectomy	Died 17 days after surgery	5 cm × 4 cm	Local metastasis	II	
Chambers and Carson[7] (1975)	43/M/L	Flank pain	None known	Radical nephrectomy	Died 9 months after surgery	Not mentioned	Liver	IV	
Axelrod et al[8] (1978)	48/M/R	Abdominal distension, weight loss, and diarrhea	None known	None	Died 1 year after tumor discovered	2200 (unsized)	Liver, spleen, bone marrow, and lungs	IV	SAP↑
Biggers and Stewart[9] (1979)	67/M/R	Physical examination	None known	Open biopsy	Died 4 months after surgery	23 cm	Lungs	IV	
Bollack et al[10] (1982)	29/M/L	Abdominal pain, anorexia, and weight loss	None known	Radical nephrectomy+chemotherapy (vincristine sulphate+methotrexate +adriamycin)	No abnormality 6 months after surgery, with local recurrence and distant metastases 3 weeks later, died 10 days later	17 cm × 12 cm × 10 cm	Pancreas	III B	
Micolonghi et al[11] (1984)	48/F/R	Flank pain	None known	Laparotomy+chemotherapy (vincristine, methotrexate, citrovorum and doxorubicin)	Died 4 weeks after surgery	12.5 cm	Lungs	IV	
Mortensen[26] (1989)	56/M/R	Flank pain and gross hematuresis	None known	Radical nephrectomy +chemotherapy (cyclophosphamide+vincristine +adriamycin+DTIC+cisplatin)	Died 18 months after surgery	4 cm	Lungs metastasis, 7 months after surgery	IA	
Acha Perez et al[12] (1993)	47/M/R	Gross hematuria and left back pain	None known	Laparotomy fail to excision	Died 3 months after surgery	8 cm × 8 cm	Local metastases	IIIB	
Ah-chong and Yip[13] (1993)	56/M/R	Abdominal pain	Right renal stone	Radical nephrectomy	Metastasis 6 months after surgery	Not mentioned	Bony metastasis 6 months after surgery	?	SAP↑
Watson et al[14] (1995)	47/M/R	Abdominal pain, loss of appetite, and lethargy	None known	Radical nephrectomy	Died 4 months after surgery	12 cm × 9 cm × 9 cm	Invasion of liver capsule	IIIB	SAP↑
Meessen et al[27] (1995)	46/M/L	Not mentioned	None known	Radical nephrectomy	Disease-free 16 months	15 cm × 9 cm × 8 cm	Left adrenal gland	IIIB	
Leventis et al[17] (1997)	67/M/L	Flank pain, gross hematuria	None	Radical nephrectomy+regional lymphadenectomy+chemotherapy	Died 4 months after surgery	28 cm × 14 cm × 10 cm	Lungs matastasis 6 weeks after surgery	IB	
Ito et al[16] (1997)	67/F/L	Physical examination	None	Radical nephrectomy	Recurrent 2 month after surgery. Died 4 months after surgery	25 cm × 18 cm × 15 cm	Local matastasis, 2 weeks after surgery	IB	
Leggio et al[18] (2006)	60/M/L	Abdominal pain	Hyperlipemia, smoking	Radical nephrectomy	Died 8 months after surgery	12 cm	Local recurrence, 7 months after surgery	IB	
Tommaso et al[19] (2007)	79/M/L	Flank pain, weakness, and loss weight	None	Radical nephrectomy+radiation therapy	Died 7 months after surgery	22 cm × 16 cm	Local recurrence and distant metastasis to diaphragm, pleura and ribs, 3 months after surgery	IIIB	SAP ↑
Lee et al[20] (2010)	71M/?	Not mentioned	Not mentioned	Biopsy+radiotherapy	Died 1.6 months after admitted	6 cm	Lungs	IV	
Puri et al[21] (2012)	65/F/L	Flank pain, gross hematuria, and occasional dysuria	Hypertensive	Radical nephrectomy +chemotherapy (adriamycin+ifosfamide and cisplatin)	Not mentioned	Not mentioned	Lungs and bladder metastasis, 1 month after surgery	?	
Antonio et al[22] (2014)	50/F/L	Pelvic and back pain	None known	Radical nephrectomy	At least 6 years	5.5 cm × 4.9 cm	None	IB	
	66/F/L	Back pain	None known	Radical nephrectomy	At least 2 years	3.5 cm × 3.2 cm × 3.2 cm	None	IA	
	78/F/L	Flank pain and macroscopic hematuria	None known	Radical nephrectomy	Died 14 months after surgery	7 cm × 6 cm × 5.1 cm	Lungs and brain metastasis, 1 year after surgery	IB	
Flynn et al[1] (2015)	77/F/L	Gross hematuria and flank pain	Not mentioned	Radical nephrectomy	Disease-free at least 2.5 years after surgery	3.3cm	None	IA	
Virgilio et al[24] (2017)	59/F/L	Abdominal distention and intestinal subocclusion	Not mentioned	Radical nephrectomy	Died 3 months after surgery	15 cm	Left colon and adrenal gland	IIIB	
Zhang et al[28] (2018)	41/M/R	Flank pain	Not mentioned	Radical nephrectomy +chemotherapy (pharmorubicin+ifosfamide +endostar)	Disease-free at least 8 months	10 cm × 9 cm × 8 cm	None	IB	
The present	48/F/L	Abdominal distension and gross hematuria	None	Radical nephrectomy+chemotherapy (ifosfamide+cisplatinum+pirarubicin) +Anlotinib	Disease-free at least 26 months	21 cm × 18 cm × 11 cm	Lungs	IV	SAP ↑

DTIC = dacarbazine, F = female, L = left, M = male, R = right, SAP = serum alkaline phosphatase.
? = Unable to evaluate.

shorter survival times for patients with osteosarcoma were associated with the expression of MSH6 as well as simultaneous nonresponse to chemotherapy and presence of metastasis.[32] The FANCF gene is part of the DNA damage repair response, Fanconi anemia-BRCA pathway, which is responsible for DNA repair by homologous recombination and maintenance of genomic stability. We consider this variant to be of unknown significance. The ERCC4 gene product plays a role in repairing the DNA damage and in maintaining genomic stability. Sun and Li found that ERCC1, 2, and 4 are significantly associated with poor response to chemotherapy and unfavorable survival of osteosarcoma.[33,34] Based on the evidence above, we suspect that this is the reason why this patient is sensitive to chemotherapy and thus has longer survival.

4. Conclusion

The present case illustrates a true primary osteosarcoma originating in the kidney without known clear risk factors. Due to the relatively small number of cases reported in the current literature, there are not enough data to support the early diagnosis and treatment of this tumor. The combination of surgical resection (with the achievement of negative surgical margins) and chemotherapy may be the best current treatment for the disease, compared to surgery or chemotherapy alone, slowing the progression of the disease, reducing the frequency of recurrence, and prolonging the OS.

Author contributions

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Resources: Changkun Huang, Xuan Zhu, Xiaokun Zhao.
Validation: Xiaokun Zhao.
Writing – original draft: Changkun Huang.
Writing – review & editing: Ran Xu.

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