Primary renal extra-osseous osteosarcoma

Kevin J. Flynn,* MD,[1] Hristos Z. Kaimakliotis,* MD,[1] Liang Cheng, MD,[2] Chandru P. Sundaram, MD[1]

[1]Department of Urology, Indiana University School of Medicine, Indianapolis, Indiana, USA

[2]Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, Indiana, USA

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Primary renal extra-osseous osteosarcoma is an exceedingly rare and deadly kidney neoplasm with only 27 reported cases to date. Extra-osseous osteosarcoma is a mesenchymal sarcoma that produces osteoid, but has no skeletal or periosteal involvement and most commonly arises in the lower extremities. Yet, it can arise in other locations such as the kidney. Extra-osseous osteosarcoma behaves as a separate entity from osseous osteosarcoma and should be treated as such. The treatment is surgical resection. Five year overall survival is 46% for local and 10% for metastatic disease. Additionally, 45%-50% of patients experience disease recurrence. We present a 77-year-old woman who underwent work up for recurrent gross hematuria and subsequently underwent radical nephroureterectomy for presumed upper tract urothelial cell carcinoma. However, pathologic analysis revealed a diagnosis of primary renal extra-osseous osteosarcoma. She is alive with no evidence of disease 30 months after surgery.

Key Words: osteosarcoma, prognosis, soft tissue sarcoma, kidney cancer, nephrectomy

Introduction

Extra-osseous osteosarcoma is a rare and aggressive malignancy that accounts for 1% of soft tissue sarcomas and < 4% of all sarcomas.[1-4] Specifically, extra-osseous osteosarcoma arising in the kidney is especially rare with only 27 reported cases.[5] Extra-osseous osteosarcoma is a malignant mesenchymal neoplasm that produces osteoid and sometimes cartilage without skeletal or periosteal involvement.[1-3,5] The exact histeogenesis of extra-osseous osteosarcoma is not fully understood. There are multiple different histologic subtypes with pleomorphic osteosarcoma being the most common.[5] Extra-osseous osteosarcoma most commonly presents in the lower extremity as a palpable and expanding soft tissue mass.[1-4] Lesions arising in the retroperitoneum commonly present with flank pain.[2,5] Mean tumor diameter at time of diagnosis is around 7 cm-10 cm.[2-4] Imaging typically demonstrates extensive calcification.[2,3,5,6] The differential diagnosis for primary renal extra-osseous osteosarcoma includes renal cell carcinoma, upper tract urothelial cell carcinoma, oncocytoma, and other less common kidney neoplasms.

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*denotes co-first authors

Address correspondence to Dr. Kevin J. Flynn, Department of Urology, Indiana University Simon Cancer Center, 535 Barnhill Drive, Suite 150, Indianapolis, IN 46202 USA

Case report

A 77-year-old female presented with gross hematuria and left flank pain. Cross-sectional imaging was notable for a heterogeneous filling defect in the left renal pelvis extending into multiple calyces with irregular dystrophic calcification, concerning for urothelial cell carcinoma, Figure 1. Further evaluation with ureteroscopy revealed a solid non-papillary yellow mass originating from the renal pelvis. Biopsy and brushings were deemed insufficient for a definitive diagnosis, although cytology was suspicious for high-grade urothelial carcinoma. The patient underwent an uncomplicated left robotic-assisted laparoscopic radical nephroureterectomy and hilar lymph node dissection. Surgical pathology revealed a high grade 3.3 cm osteosarcoma originating in the left renal pelvis with invasion into the renal parenchyma. None of the lymph nodes were involved. Immunohistochemistry (IHC) supported the diagnosis with stains for cytokeratin AE1/AE3, p63, high-molecular weight cytokeratin, S100 protein, PAX-2, and HMB-45. Extensive metastatic

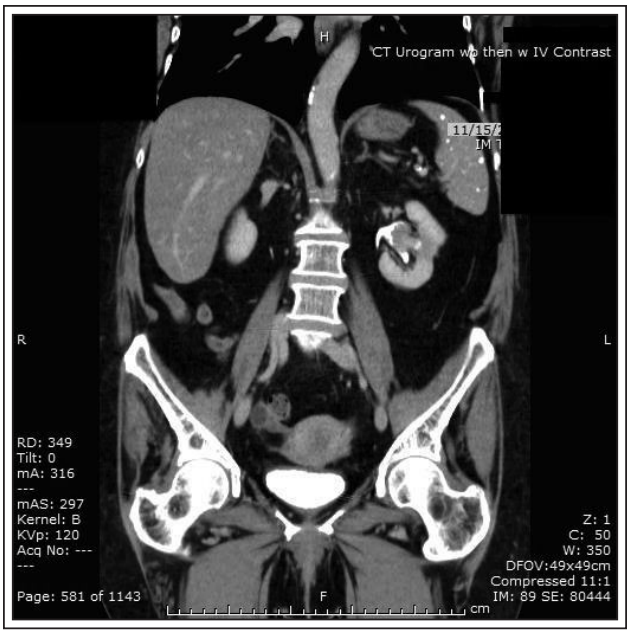

Figure 1. Left collecting system filling defect during delayed images.

work-up after definitive diagnosis was negative. The patient did not undergo any adjuvant therapy, and remains disease-free 2.5 years later.

Discussion

Primary renal extra-osseous osteosarcoma is a rare, but aggressive and deadly malignancy. Published reports indicate that extra-osseous osteosarcoma should be treated as a separate entity from osteosarcomas arising in bone.[4] Stark differences in age of presentation and extra-osseous osteosarcoma's relative chemoresistance compared with its skeletal counterpart support this claim. Small retrospective studies of extra-osseous osteosarcoma report a mean age ranging between 50-55.[1-5,7] This is in contrast to a younger population in osteosarcoma of the bone. Multiple studies demonstrate an increased incidence of extra-osseous osteosarcoma in men,[1-4] and previous trauma and radiation exposure as well-documented risk factors.[1-3,7]

The lower extremitiy is the most common location of origin of extra-osseous osteosarcoma and presents as a palpable expanding soft tissue mass.[1-4] For patients who have extra-osseous osteosarcoma in the retropertonium, flank pain is a common presentation.[2,5] At time of diagnosis, extra-osseous osteosarcoma tumors are typically 7 cm-10 cm in diameter. The calcification present on imaging is described as a "sunburst" appearance.[2,3,5,6] The CT urogram in our case illustrated dystrophic calcification consistent with extra-osseous osteosarcoma, but given the heterogeneous filling defect and the rarity of extra-osseous osteosarcoma, urothelial cell carcinoma was the presumed diagnosis.

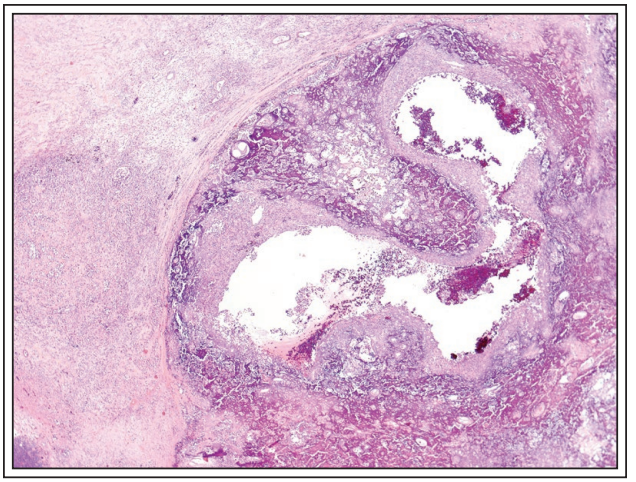

Figure 2. Primary renal extra-osseous osteosarcoma. H&E, reduced from x100. Multinucleated osteoclasts within a matrix of mitotic spindle cells, and patches of osteoid and visible areas of necrosis.

Microscopic examination with H&E stain demonstrates malignant anaplastic spindle cell proliferation with interspersed osteoid of variable calcification, Figure 2 and 3.[3,5,8] Giant multinucleated cells are noted, with high cellularity, nuclear pleomorphism, and high mitotic activity.[1-3,5] IHC of extra-osseous osteosarcoma is notable for vimentin, osteonectin, osteocalcin, and

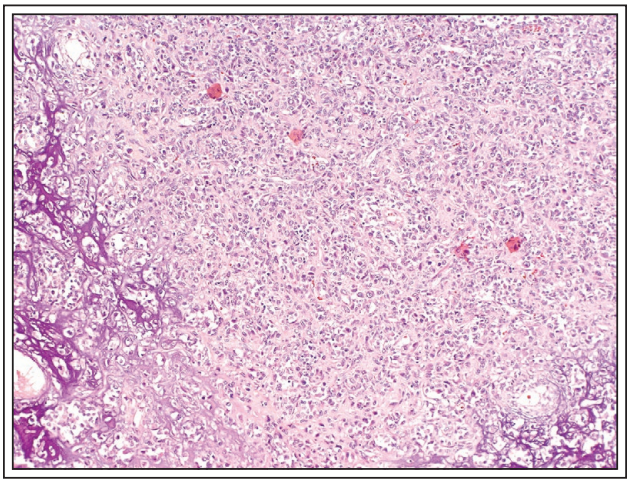

Figure 3. Extra-osseous osteosarcoma. H&E, reduced from x200. Cells with visible nuclear pleomorphism and interspersed areas of osteoid.

CD- 99. However, the role of IHC role in extra-osseous osteosarcoma is debated, advocated for by Zhang et al in order to avoid misdiagnosis of other tumors capable of producing bone or cartilage, whereas Lopez-Beltran et al question its utility due to the amount of time needed to prepare the sample.[5,7]

Surgical resection with clear margins is the mainstay of treatment, with an unclear role for chemotherapy and radiation.[1-3, 5-7] Unlike osteosarcoma arising in the bone, extra-osseous osteosarcoma does not have a strong response to cisplatin-based chemotherapy, however some reports postulate that ifosamide may be beneficial.[1,3,4] Lopez-Beltran et al suggest that in organ confined and low stage tumors surgical resection alone may be sufficient,[5] and tumor size < 5 cm may also been a positive predictor.[2]

Prognosis is poor and the rate of recurrence, both local and distant, is high, approximately 45%-50%, with roughly 20% of patients presenting with metastases at diagnosis.[2,3] Five-year survival in patients presenting with localized disease was 46%, compared to 10% in those with metastatic presentation.[1] For extra-osseous osteosarcoma originating in the kidney, median survival is 15 months, and this is likely attributed to advanced stage at time of presentation, with 92% of patients presenting with T3-4 disease.[5]

Extra-osseous osteosarcoma of the kidney is an exceedingly rare, chemo-resistant, and highly fatal malignancy that behaves as a separate entity from osteosarcoma of the bone. Rare entities still exist in the differential for upper tract lesions, although management does not appear to be affected with regards to need for extirpative surgery. □

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