Urology Case Reports 31 (2020) 101187

Contents lists available at ScienceDirect

Urology Case Reports

journal homepage: http://www.elsevier.com/locate/eucr

Pediatrics

Primary renal Ewing Sarcoma masquerading as Wilms in an adolescent female

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ARTICLE INFO

Keywords:
Pediatric
Renal cell carcinoma
Minimally invasive

ABSTRACT

Primary renal Ewing's sarcoma (ES) of the kidney represents a rare oncologic entity belonging to the collection of small round cell tumors, which typically feature osseous presentations. Renal ES is an aggressive disease entity with high metastatic potential, either at time of presentation or following initial extirpative therapy. Herein, we report the case of a 14-year-old female who initially presented with intermittent gross painless hematuria and a large left renal mass identified on ultrasound and confirmed on follow up MRI. Following partial nephrectomy (PN), patient was diagnosed with primary renal ES and subsequently underwent completion nephrectomy and chemotherapy.

Introduction

Primary renal Ewing's Sarcoma of the kidney is a rare, aggressive oncologic entity. We report on a case of primary renal Ewing Sarcoma, which initially masqueraded as a Wilms tumor in an adolescent female. Following initial partial nephrectomy, patient underwent completion nephrectomy and chemotherapy with no evidence of disease at 3-month follow-up.

Case report

An otherwise healthy 14-year-old female presented with intermittent gross painless hematuria with negative urine culture. She denied voiding symptoms, weight loss, fever, or flank pain, and physical exam was unremarkable. Family history was significant for an uncle with clear cell renal cell carcinoma (ccRCC) s/p PN at 46 years old and a second cousin with chromophobe RCC s/p radical nephrectomy at 54 years old. Ultrasound demonstrated a 6 cm heterogeneous left renal mass without significant blood flow (Fig. 1). Follow-up MRI demonstrated a 5.6 cm left mid/lower pole renal mass with minimal enhancement (Fig. 2).

In order to preserve maximum renal function for possible chemotherapy, left laparoscopic PN was planned with presumptive diagnosis of ccRCC based on family history versus isolated Wilms tumor versus oncocytoma. PN was performed on clamp (warm ischemia ~22 minutes) and tumor was enucleated with an estimated blood loss of 125 cc. Given possible diagnosis of Wilms tumor, an intra-operative frozen section of resected tumor was collected which demonstrated features compatible with blastemic Wilms tumor. As patient was now Stage III for presumed Wilms along with negative gross margins on specimen, decision was made to perform hilar node dissection and defer radical nephrectomy as patient would still require radiation therapy. Patient tolerated the operation well and was discharged on day #3 with plan to initiate chemoradiotherapy as an outpatient.

Final histopathology later demonstrated undifferentiated malignant small round blue cell tumor with EWSR1-FLI-1 fusion gene rearrangement consistent with renal ES (Fig. 3). Renal parenchymal margin was negative with a distance of <0.1 cm from tumor with presence of a pseudo-capsule, though tumor invasion of the renal sinus was present. All ten lymph nodes (LN) from the left peri-aortic and hilar regions were negative.

Following discussion with pediatric oncology, patient underwent metastatic evaluation with PET-CT and CT chest; imaging was negative for metastatic disease and residual renal disease. Given extremely aggressive nature of renal ES, patient underwent left laparoscopic completion nephrectomy. Patient tolerated procedure well and was discharged on postoperative day #1. Histopathology of the completion nephrectomy specimen demonstrated no evidence of residual disease and one additional LN was negative for disease.

Following ovarian harvest by reproductive endocrinology, the patient was enrolled in clinical trial AEWS1221 and randomized to regimen A, consisting of vincristine, doxorubicin, and cyclophosphamide alternating with etoposide and ifosfamide. She currently has no

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https://doi.org/10.1016/j.eucr.2020.101187
Received 21 March 2020; Accepted 1 April 2020
Available online 8 April 2020

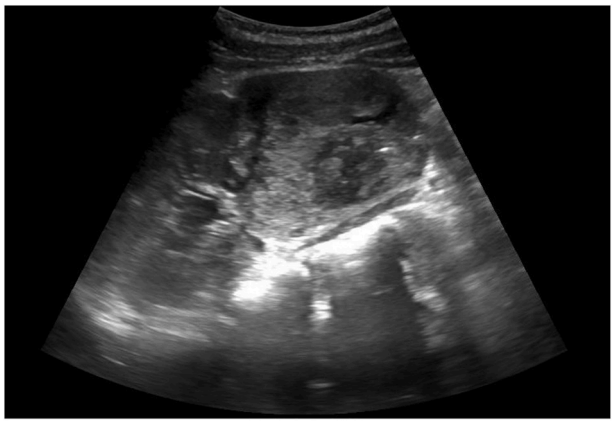

Fig. 1. Renal Ultrasound Left Renal Mass is demonstrated with a heterogeneous appearance.

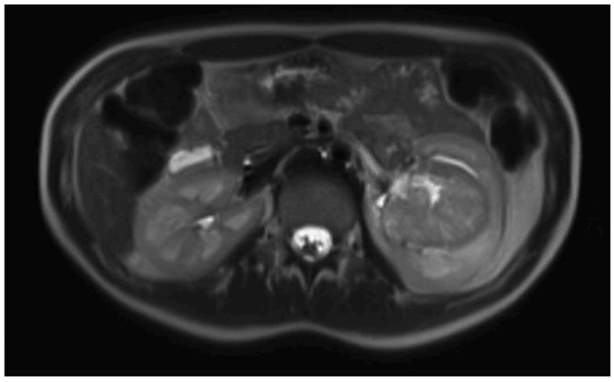

Fig. 2. T2 Axial MRI. Renal mass is located on/within the left lower pole.

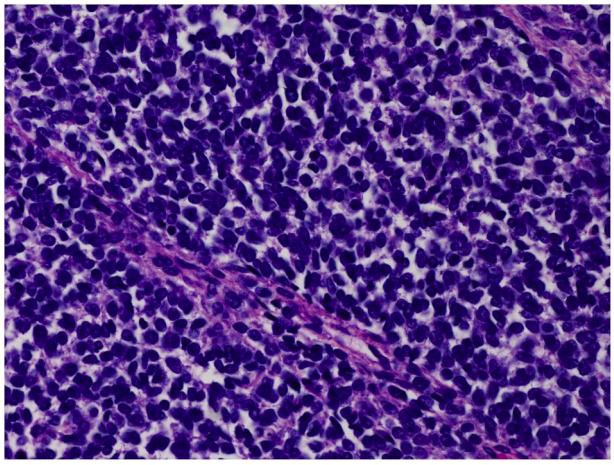

Fig. 3. H&E Stain Magnification ×40. The tumor is highly cellular and shows sheets of undifferentiated round cells. (Color online, black and white in print). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

evidence of disease at completion of induction chemotherapy, 3 months post-operative. Additional genetic testing demonstrated a heterozygous ATM mutation in patient's germ line, a gene mutation previously shown to convey elevated cancer risk, particularly for breast and pancreatic cancer. Patient's mother was also shown to possess a heterozygous ATM mutation.

Discussion

Ewing sarcoma of the kidney represents a rare disease entity, with approximately 100 prior cases in the literature, and predominantly affects young adult males. While most renal masses are identified incidentally on cross-sectional imaging, renal ES typically presents symptomatically. Predominantly, the majority of patients present with pain or hematuria, as our patient did, with other patients presenting with palpable renal masses, dysuria, fevers, or weight loss.[1,2] Cross sectional imaging does not yield definitive diagnosis, demonstrating large heterogeneous masses, frequently with internal hemorrhage, necrosis, and diffuse large calcifications.[2] However, these radiological features are also common to other renal masses, such as renal cell carcinoma.

Definitive diagnosis is typically made based on histological examination utilizing immunohistochemical staining and genetic analysis. Microscopy demonstrates small round blue cells arranged in sheets with immunohistochemical staining positive for CD99.[3] FISH analysis may demonstrate multiple diagnostic translocations with the most common being a (11; 22) (q24; q12) translocation resulting in a EWSR-FLI-1 fusion gene, with a t (21; 22) resulting in a EWS-ERG gene fusion also being possible.[3] Additionally, it has been demonstrated that mutations in DNA repair genes, such as ATM, are enriched in patients with Ewing Sarcoma, however, the exact significance is unknown.[4]

Extirpative therapy followed by chemotherapy is the mainstay of treatment, with the vast majority of patients having undergone radical nephrectomy[1,2,5] Chemotherapy regimen is typically dictated by current treatment guidelines for ES; our patient enrolled in a trial designed for treatment of metastatic ES (AEWS1221). Prognosis is poor, with estimated median overall survival ranging from 26.5 to 40 months for those patients without metastatic disease at presentation to 5.6 months for those patient with locally advanced metastatic disease.[1,2] Additionally, 35% of patients initially present with metastatic disease, and an additional 40% of patients develop metastatic disease after extirpative therapy.

Unique to our case was the decision to initially approach this mass via laparoscopic PN. Previously, multiple authors have reported success in managing Wilms tumor with nephron sparing surgery and PN is well-established for the management of renal cell carcinoma, with excellent oncologic and functional outcomes. Of note, we were able to achieve negative surgical margins following PN as well as no evidence of residual disease on radical nephrectomy, with minimal morbidity and short hospital stay. However, given the highly aggressive nature of renal ES and with only one prior report of robotic partial nephrectomy in the oncological literature,[5] decision was made to perform laparoscopic completion nephrectomy. To our knowledge, this is the first reported case of Ewing Sarcoma managed initially with laparoscopic partial nephrectomy.

Conclusion

Renal ES is a rare renal malignancy that typically presents in young adults and is primarily identified following symptom development, most commonly pain and hematuria. Renal ES remains a highly lethal disease, further complicated by challenges in diagnosis with no distinct radiological or symptomatic presentation. Definitive diagnosis is established via histological and genetic features, with ESWR rearrangement present in the majority of patients. Management is multidisciplinary with most cases requiring surgical and chemotherapeutic treatment, with radiation typically reserved for unresectable disease and positive surgical margins.

Declaration of competing interest

Dr. Kavoussi has previously received stock options from InTouch Health for his role as a consultant. Dr. Kozel, Dr. Reifsnyder, Dr.

Griffiths, and Dr. Gitlin have no declarations of interest to disclose.

CRediT authorship contribution statement

Zachary M. Kozel: Conceptualization, Writing - original draft. **Jennifer E. Reifsnyder:** Supervision, Writing - review & editing. **Luke Griffiths:** Writing - review & editing. **Jordan S. Gitlin:** Writing - review & editing, Investigation. **Louis R. Kavoussi:** Conceptualization, Investigation, Writing - review & editing, Supervision.

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