J Cancer Allied Spec 2024;10(1):5

Case Report

Pediatric Ewing Sarcoma of Kidney: A Case Series and Review of Literature

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Received: 10 July 2023/Accepted: 29 September 2023

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Citation: Salim A, Ali S, Latif T. Pediatric Ewing Sarcoma of Kidney: A Case Series and Review of Literature. J Cancer Allied Spec [Internet]. 2024;10(1):1-7. https://doi.org/10.37029/jcas.v10i1.563

Funding: None.

Competing interest: The author(s) declare(s) that there is no conflict of interest.

Abstract

Introduction: Renal Ewing sarcoma is an aggressive and rare malignancy affecting children and adolescents. Limited data on its management contribute to uncertainties in treatment. **Case description**: We present two pediatric cases of renal Ewing sarcoma. Both cases emphasize the significance of accurate diagnosis, multimodal treatment, and long-term follow-up in achieving favorable outcomes. Accurate diagnosis of renal Ewing sarcoma is crucial for effective management. Multimodal treatment involving neoadjuvant chemotherapy, surgical resection and staging with lymph node sampling, and chemotherapy continuation has shown promising results in our cases. Long-term follow-up is essential for monitoring disease progression and ensuring optimal outcomes. **Practical Implications:** There is limited data published about these renal tumors, especially in the pediatric population, and most studies lack long-term follow-up, with uncertain management due to limited data. This data will add to the newer, multimodal approach and form the basis for future meta-analysis to help formulate guidelines for upcoming international meetings. Continued research efforts are necessary to optimize strategies and improve the prognosis for pediatric patients with renal Ewing sarcoma.

Keywords: Cancer, case report, Ewing sarcoma, pediatrics, renal

Introduction

The Ewing sarcoma family of tumors (ESFTs) are aggressive malignancies characterized by small, round blue cells and are typically observed in children and adolescents. While bone is the most prevalent location for these tumors, occurrences at sites outside the bone are uncommon but recognized.[1] In 1975, Seemayer *et al*. reported the first documented case of ESFT originating in the kidney, which remains an exceptionally rare diagnosis.[2] It is common for ESFT in the kidney to be misdiagnosed or experience delayed diagnosis due to similarities with more prevalent small round cell tumors in childhood, such as Wilms tumor or rhabdoid tumor of the kidney.[3]

Ewing sarcoma/primitive neuroectodermal tumor of the kidney (PNET) is an extremely aggressive tumor. Around 20% of individuals with osseous Ewing sarcomas are diagnosed with metastatic disease, with 44% showing lung

metastases exclusively, while 51% have bone or bone marrow involvement (with or without lung metastases). Additionally, 5% of patients present with metastases in other organs.[4] The median age of presentation, as reported in the literature, is 26 years.[5]

There is limited published data available on renal tumors such as Ewing sarcoma and PNET, and most studies lack long-term follow-up.[6,7] The existing data primarily focus on young adults, and a meta-analysis conducted in 2020 identified reporting bias, incomplete analysis, and variations in age groups.[8] While the treatment for adults with this tumor is well documented in international literature, there is no consensus on treating pediatric patients due to the rare incidence and limited literature available.[8] Regional literature reports age groups ranging from 18 months to 13 years, with short-term follow-up.[6,7]

This paper presents two cases – a 4-year-old boy and a 15-year-old girl – diagnosed with Ewing sarcoma of the kidney. The cases were reviewed and approved by the local Institutional Review Board Committee.

Case Description

Case 1

A 4-year-old boy, previously healthy with no pertinent family history, presented through clinic with complaints of right-sided flank pain for a week, and imaging done already (computed tomography [CT] scan abdomen) showed a right retroperitoneal mass measuring 14 × 12.5 cm and labeled as a right-sided Wilms tumor.

Case 2

A 15-year-old girl presented through clinic with a history of intermittent abdominal pain and distention for 1 year. Her CT scan of the abdomen showed a right retroperitoneal mass measuring 15 cm and labeled as a right-sided Wilms tumor. She was previously healthy and had a family history of diabetes mellitus.

Diagnosis and management

Case 1

The boy underwent an image-guided biopsy, which revealed a malignant round blue cell tumor [Figure 1] (CD-99 and FLI-1 positive) and labeled Ewing sarcoma. Nuclear scanning revealed a non-functioning right kidney, and staging workup revealed metastatic disease (sternum, D4 vertebra) and a solitary nodule in the lung (left upper lobe).

The case was discussed in a multidisciplinary team meeting, and according to EE 99 (Euro-EWING 99 trial[9]), the child received six cycles of VIDE (vincristine, ifosfamide, doxorubicin, and etoposide). During this time, the child developed mild cardiac dysfunction, which was treated medically. For the subsequent cycles, doxorubicin, a cardiotoxic drug, was replaced by actinomycin. Reassessment scans showed a grossly stable disease. The patient underwent a right radical nephrectomy. The histopathology showed 100% tumor necrosis with clear margins. Subsequently, the boy received radiation therapy for the sternum and D4 vertebra. Furthermore, he continued to undergo chemotherapy and received eight cycles of the VAI (vincristine, actinomycin, and ifosfamide)

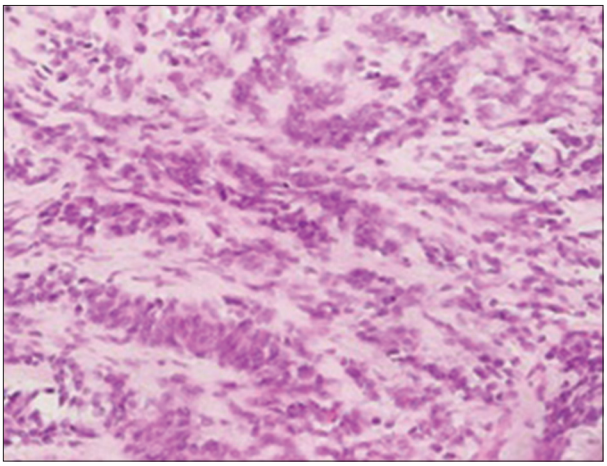

Figure 1: Section on trucut biopsy reveals tissue cores comprising of a malignant round blue cells neoplasm. The tumor comprises sheets of small to medium-sized cells with hyperchromatic nuclei, inconspicuous nuclei, and moderate to scant cytoplasm

protocol with the omission of actinomycin during the radiation treatment.

The child was kept on routine follow-up; reassessment scans showed reduced uptake in D4 and sternum, the lung nodule resolved, and cardiac function improved. He is currently 12 years old, clinically well, and school-going, and has had no evidence of relapse in 8.5-year post-treatment.

Case 2

She underwent an image-guided biopsy, revealing a malignant round blue cell tumor (CD99 and NKX2.2 positive) labeled Ewing Sarcoma. Her metastatic workup was negative. The tumor was 16.8 cm × 12.7 cm × 18.6 cm in size, with an inferior vena cava tumor thrombus.

The case was discussed in the multidisciplinary team meeting, and neoadjuvant chemotherapy was planned according to the AEWS1031 protocol of the children oncology group. The child was started on compressed chemotherapy, i.e., six cycles of vincristine, doxorubicin, cyclophosphamide (VDC), and ifosfamide/etoposide (×2 weekly). Following this, she underwent reassessment scans, which showed a partial response to chemotherapy, including clearance of the tumor from the inferior vena cava. The patient subsequently underwent a right radical nephrectomy. Histopathology showed 85% necrosis [Figure 2], with a viable tumor in the renal sinus and negative margins. She received further chemotherapy (a total of 17 cycles according to protocol). The patient is now 17 years old and at 1.5-year follow-up, disease-free, clinically well, and school-going.

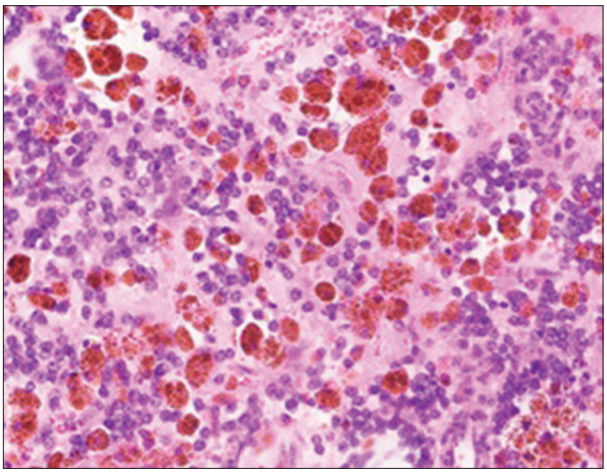

Figure 2: Sections from the radical nephrectomy specimen show sheets of malignant round blue cells with hyperchromatic nuclei, inconspicuous nuclei, and moderate to scant cytoplasm. Background shows extensive necrosis and hemorrhage

Discussion

Ewing sarcoma rarely presents as a primary kidney tumor, and clinical symptoms are often non-specific, such as abdominal or flank pain, hematuria, and a palpable mass. Imaging findings are typically indistinct, with central necrosis and hemorrhage being common. Pre-operative diagnosis of renal Ewing sarcoma is challenging, and post-operative histopathology is usually necessary for confirmation. Histologically, renal Ewing sarcoma is characterized by uniform, small, round cells. Differential diagnoses for this kidney histomorphology include Wilms tumor, malignant lymphoma, synovial sarcoma, alveolar rhabdomyosarcoma, clear cell sarcoma, small-cell neuroendocrine carcinoma, desmoplastic small round blue cell tumor, and small cell carcinoma.

Several approaches can be employed to diagnose PNET, including light microscopic examination of tumor tissue, immunohistochemistry, electron microscopy, genetic investigation, and molecular biologic examination. These tumors are composed of primitive round cells with high nucleus-to-cytoplasmic ratios. Immunohistochemically, PNET demonstrates positive staining for CD99. However, CD99 expression is not specific to PNET among round-cell tumors. While FL-1 can serve as a variable immunohistochemical marker for PNET, it is also positive in lymphoblastic lymphoma, while other small cell tumors are negative. On the other hand, WT-1 is a positive immunohistochemical marker for Wilms tumors and desmoplastic round cell tumors, but it is negative for PNET, neuroblastoma, and rhabdomyosarcoma.[10]

For the diagnosis of Ewing sarcoma in unusual locations (such as the kidney), performing FISH for EWSR1 rearrangement is recommended. However, these were not performed on our patients, which is a limitation of this report.

The presence of metastasis at the time of diagnosis has been noted to carry the greatest prognostic significance with regard to survival for patients with the Ewing Sarcoma family of tumors. Protocol AEWS0031 from the Children's Oncology Group treated patients with localized Ewing sarcoma with VDC/IE chemotherapy and local control. The 5-year event-free survival (EFS) rates were 67% and 74%, depending on the cohort dosing frequency.[11] In contrast, the Euro-EWING 99 trial analyzed dose-intensive chemotherapy outcomes in the primary disseminated multifocal Ewing Sarcoma family of tumors (excluding isolated pulmonary metastases) and reported EFS and overall survival (OS) at 3 years for 281 patients as 27 ± 3% and 34 ± 4%, respectively.[12]

While the overall rates of metastases at diagnosis for all patients with the Ewing Sarcoma family of tumors have been reported as 22–36%, the specific population with renal primary Ewing Sarcoma demonstrated a higher rate of metastases at diagnosis, at 53.2%.[2,3] Population studies have consistently found pulmonary metastases to be the most frequent site of disease spread. Outcomes analyses have suggested a relatively better prognosis for patients with pulmonary metastases, with OS ranging from 29% to 52%. In comparison, patients with metastases in other sites, such as the bone marrow, have shown OS rates below 30%.[11,12]

There is a dearth of research available on renal tumors in the pediatric population, with the majority of studies lacking comprehensive long-term follow-up data.[6,7,13]

Lymph node staging plays a crucial role in the evaluation and risk stratification of patients with the Ewing Sarcoma family of tumors. An analysis of the Surveillance, Epidemiology, and End Results Program database by Applebaum *et al*. found that patients with primary extraskeletal tumors had higher rates of regional nodal involvement compared to those with primary skeletal disease (12.4% vs. 3.2%).[14] In a study focusing on patients with primary renal Ewing sarcoma, Zöllner *et al*. reported a lymph node involvement rate of 33.3% based on the German database of GPOH Ewing sarcoma trials. A literature analysis involving 156 patients demonstrated lymph node involvement in 42.9% of cases.[15]

Due to the diverse chemotherapy protocols used in treating the Ewing Sarcoma family of tumors, it is challenging to assess the relative efficacy of these protocols. The outcomes of megatherapy studies for this tumor type have shown variable results, with some studies suggesting an improvement in EFS while others do not.[16]

The patients treated at our institution received two different protocols for treatment; one case was treated 8 years ago and the other more recently, so the protocols used were those that the treating physician deemed fit per multidisciplinary team meeting discussions. This is a bias of this report and further necessitates the need to document local literature and evaluate what protocols may be more beneficial for our population. We have compared our results with the locoregional and international literature [Table 1].

Patients diagnosed with Ewing sarcoma/PNET with clinically detectable metastatic disease at presentation generally have a poorer prognosis for EFS when treated with conventional chemotherapy, radiation therapy, and surgery. Among these patients, those with isolated pulmonary metastases tend to have a slightly better outcome, with an approximately 30% survival rate. In contrast, patients with bone or bone marrow metastases at initial diagnosis have a lower survival rate of 20% or less.[4,17] The 5-year disease-free survival rate in cases of PNET is reported to be 45-55% but the prognosis for patients with renal PNET is worse.[18-20]

Renal Ewing sarcoma has historically been associated with an aggressive clinical course, and

Table 1: Summary of comparison between the current study cases and previously published cases

Case	References	Age at diagnosis (years)	Gender	Presenting complaint	Side of tumor	Size of tumor at diagnosis (cm)	Extent	Approach	Surgical intervention
1	Areej *et al.*	4	Male	Right sided Flank pain	Right	14.0×12.5	Localized	Neoadjuvant chemotherapy	Right radical nephrectomy+Retroperitoneal lymph node sampling
2	Areej *et al.*	15	Female	Right sided Flank pain and abdominal distension	Right	16.8×18.6	Localized	Neoadjuvant chemotherapy	Right radical nephrectomy+Retroperitoneal lymph node sampling
3	Mahwish *et al.*[13]	6	Female	Abdominal Distension	Left	6.5×5.0	Localized	Upfront surgery	Left nephrectomy
4	Badar *et al.*[6]	13	Female	Abdominal pain and hematuria	Right	6.0×9.0	Metastatic (Liver, Lungs)	Upfront surgery	Right radical nephrectomy
5	Bradford *et al.*[8]	16	Male	Abdominal pain-initially diagnosed as Wilms Tumor	Right	Not known	Not known	Upfront surgery	Right partial nephrectomy
6	Bradford *et al.*[8]	11	Male	Abdominal pain	Left	17×7.3	Multiple bone deposits	Upfront surgery	Left nephrectomy
7	Citak *et al.*[16]	13	Female	Generalized bone pain	Left	04×03	Multiple bone deposits	Neoadjuvant chemotherapy	Left nephrectomy

Case	Tumor weight	Margins	Lymph node status	Treatment received	Radiation dose	Recurrence status	Time lapsed between treatment and relapse	Outcome	Molecular Data
1	900 grams	Negative (1.2 cm from vessel and 7.4 cm from ureter)	4 lymph nodes sampled-not involved	E99 protocol VIDE x8	4500 cGY	None (8 years)	Not applicable	Disease-free survival>5 years	Not available
2	980 grams	Negative (1 cm margin from vessel and ureter)	3 lymph nodes sampled-not involved	AEWS0031 protocol VDC/Ifosfamide/etoposide×17	Not recommended	None (1 year)	Not applicable	Disease free survival>1 year	Not available
3	Not available	Not available	Not sampled	Euro Ewing Protocol	Not done	Not known	Not known	Not followed	Not available

(Contd...)

Table 1: ***(Continued)***

Case	Tumor weight	Margins	Lymph node status	Treatment received	Radiation dose	Recurrence status	Time lapsed between treatment and relapse	Outcome	Molecular Data
4	Not available	Negative	Not sampled	Euro Ewing Protocol	50 Gy	Relapse (lungs)	21 months	Expired 5 months after relapse	Not available
5	Not available	Not available	Not sampled	PARP inhibitor trial	Given in relapse to lungs 20 Gy, liver 40 Gy, femur 20 Gy and ileum 20 Gy	Relapse to lungs, liver, and bone	13 months	Expired at 5.8 years with active disease	EWSR1 rearrangement
6	Not available	Not available	Not sampled	VDC/IE; auto SCT. everolimus	Not done	Relapse (site not specified)	4.5 years	Alive with disease	EWSR1 Rearrangement
7	Not available	Not available	Not sampled	European protocol (EICESS 92)	Not done	Relapse (pre-auricular mass)	11 months	Expired 4 months after relapse with active disease	EWSR1 Rearrangement

special care should be taken when evaluating renal tumors due to the radical differences in treatment and prognosis compared to other tumors in the differential diagnosis. Our cases highlight the importance of accurate diagnosis, multimodal treatment, surgical staging, and long-term follow-up in achieving favorable outcomes. Further research is needed to optimize strategies for pediatric patients with renal Ewing sarcoma.

Acknowledgment

None.

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Author Contributions

Conceived and designed the analysis: AS, SA, TL; Collected the data: AS; Contributed data or analysis tools: AS; Performed the analysis: AS; Wrote the paper: AS, SA, TL.