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Ewing Sarcoma Beyond the Bone: A Rare Primary Renal Presentation

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Simple Summary

Ewing sarcoma is a rare and aggressive cancer that usually arises in bones and primarily affects children and young adults. In very uncommon cases, it can develop in organs outside the skeleton, which makes diagnosis particularly challenging. One of the rarest locations is the kidney, where the tumor may mimic more common renal cancers and delay appropriate treatment. In this report, we describe a rare case of Ewing sarcoma originating in the kidney of an adult patient. We highlight the importance of combining medical imaging, tissue examination under the microscope, and molecular genetic testing to establish an accurate diagnosis. The case also demonstrates the role of multidisciplinary care, including surgery and systemic chemotherapy, in achieving disease control. By documenting this unusual presentation, our study contributes to the limited knowledge about renal Ewing sarcoma and may help clinicians recognize and manage similar cases more effectively.

Abstract

Background: Primary renal Ewing sarcoma (ES) is an exceptionally rare and aggressive malignancy, posing significant diagnostic and therapeutic challenges in adults. Clinical presentation is often nonspecific, frequently resulting in delayed diagnosis and early metastatic dissemination. **Methods:** We report a case of a 45-year-old woman presenting with right lumbar pain and hematuria. Imaging included ultrasound and magnetic resonance imaging, revealing a well-demarcated multicystic lesion of the right kidney. Partial nephrectomy was performed, followed by histopathology, immunohistochemistry, and molecular analysis using fluorescence in situ hybridization to confirm ES breakpoint region 1 (EWSR1) rearrangement. Subsequent management included right nephrectomy and systemic chemotherapy following the vincristine, doxorubicin, cyclophosphamide/ifosfamide, etoposide (VDC/IE) protocol. **Results:** Histopathology demonstrated sheets of small round cells with Homer-Wright rosettes and strong membranous CD99 expression. Molecular testing confirmed EWSR1 rearrangement. The patient tolerated surgery and chemotherapy well, with no evidence of recurrence or metastasis at six-month follow-up. The case highlights the critical role of integrated imaging, histopathology, immunophenotyping, and molecular diagnostics in establishing the diagnosis of primary renal ES. **Conclusion:** Primary renal ES in adults requires a high index of suspicion, multidisciplinary evaluation, and personalized therapeutic strategies.

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Surgical resection combined with systemic chemotherapy can achieve disease control. Early recognition, molecular confirmation, and interdisciplinary coordination are essential to optimize outcomes in this rare malignancy.

Keywords: Ewing sarcoma; primary renal tumor; extraskeletal; EWSR1; nephrectomy; VDC/IE chemotherapy; molecular diagnostics; adult sarcoma; small round blue cell tumor; rare malignancy

1. Introduction

Primary renal Ewing sarcoma (ES) is an aggressive malignant tumor predominantly affecting adolescents and young adults. It accounts for 10–15% of all bone sarcomas and is exceptionally rare in adults. ES can mimic other renal "small round blue cell" neoplasms, creating significant diagnostic challenges [1]. First described by James Ewing in 1921, the term "Ewing sarcoma" encompasses classic osseous ES, extraskeletal ES, Askin tumor, and primitive neuroectodermal tumors of soft tissue origin, all arising from mesenchymal progenitor cells with overlapping histological and immunohistochemical features. ES most frequently involves the pelvis, axial skeleton, and femur, though it may arise in virtually any bone or soft tissue. Patients typically present with pain, swelling, or stiffness, occasionally accompanied by systemic symptoms such as fever or weight loss, which often indicate metastatic disease. About 20% of patients present with metastases, commonly affecting the lungs or pleura [2]. Extraskeletal ES is exceedingly rare, with an incidence of 0.4 per million, roughly ten times lower than osseous ES [3]. Its age distribution is bimodal, peaking in children under 5 years and adults over 35 [4]. Common extraskeletal sites include the paravertebral region, lower extremities, head and neck, and pelvis, whereas rarer locations include the retroperitoneum, omentum, orbit, skin, and chest wall. Secondary bone involvement is uncommon [5,6].

ES is driven by chromosomal translocations generating oncogenic fusion genes. The t(11;22)(q24;q12) (~85% of cases) produces EWS-FLI1, while t(21;22)(q21;q12) and other rare rearrangements produce ES breakpoint region 1—ETS-related gene fusions in 10–15% [7]. The ES breakpoint region 1—Friend leukemia virus integration 1 (EWSR1-FLI1) oncoprotein is central to tumorigenesis, though conventional chemotherapy remains effective in many localized cases [8,9]. Histologically, ES comprises small round cells with a high nuclear-to-cytoplasmic ratio, classified among childhood "small round blue cell tumors" (e.g., retinoblastoma, neuroblastoma, rhabdomyosarcoma, nephroblastoma). Cells have scant Periodic acid–Schiff (PAS) positive eosinophilic cytoplasm, with >80% strongly expressing CD99. Additional variably expressed markers include CD45, synaptophysin, chromogranin, vimentin, keratin, desmin, neuron-specific enolase, and S100. Definitive diagnosis requires molecular confirmation via fluorescence in situ hybridization (FISH) or reverse transcription polymerase chain reaction (RT-PCR) [7]. In this regard, integrating histopathology and immunohistochemistry with the clinical context is essential for narrowing the differential diagnosis of ES. Key differentials include other small round cell malignancies such as neuroblastoma, rhabdomyosarcoma, lymphoma, desmoplastic small round cell tumor, and synovial sarcoma, as well as benign conditions such as osteomyelitis, osteogenic sarcoma, and eosinophilic granuloma. Initial imaging often begins with radiography, which may reveal the characteristic periosteal "onion-skin" reaction, while staging typically relies on bone scintigraphy, magnetic resonance imaging (MRI), and computed tomography [10].

The current standard of care for both localized and metastatic ES involves an interdisciplinary approach combining systemic chemotherapy with local control through surgery, radiotherapy, or both. In the United States, standard chemotherapy alternates VDC (vincristine, doxorubicin, cyclophosphamide) with IE (ifosfamide, etoposide) [11]. Following induction, local control is typically achieved with surgery, radiotherapy, or their combination. Five-year survival ranges from 75% to 80% in non-metastatic cases, decreasing to approximately 30% in metastatic disease [12,13]. Data shows that over the past four decades, advances in local therapy and multi-agent adjuvant chemotherapy have improved outcomes for localized ES. Nevertheless, prognosis remains poor for

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metastatic disease, diagnosed in 20–25% of patients, with lungs affected in 70–80% and bone/bone marrow in 40–45% [12,14]. Relapse occurs in 30–40% of initially localized cases, rising to 60–80% when metastases are present at diagnosis. Most relapses are systemic (71–73%), followed by combined (12–18%) and local (11–15%), with five-year survival after relapse only 15–25%; local recurrences have a better prognosis than systemic ones [15–17]. Controlling systemic dissemination remains the principal therapeutic challenge.

This case report presents a rare instance of primary renal extraskeletal ES in an adult, emphasizing the diagnostic challenges and the integrated use of imaging, histopathology, immunohistochemistry, and molecular genetics. By documenting this unusual localization and treatment approach, the report contributes to the limited literature on renal ES and provides guidance for early recognition, accurate diagnosis, and multidisciplinary management of similar cases.

2. Case Presentation

2.1. Patient Information

We report the case of a 45-year-old woman with a prior history of breast carcinoma, treated with right-sided mastectomy in 2015. In early 2023, she presented with right lumbar pain, reduced physical capacity, and recurrent episodes of painless gross hematuria.

2.2. Imaging

Initial abdominal ultrasonography and subsequent MRI identified a well-demarcated lesion in the mid-portion of the right kidney, measuring 28 × 23 × 27 mm. The lesion protruded along the dorsal contour of the kidney and displayed a multicystic architecture with multiple septations, some irregular in course, and areas of nodular thickening up to 3–4 mm (Figure 1). On T2-weighted MRI sequences, the lesion exhibited mixed signal intensity, predominantly hyperintense, while the septa were markedly hypointense (Figure 2). Intralesional hemorrhage with hemoglobin degradation products was considered. No distant metastases were detected during staging. Based on imaging features, differential diagnosis included renal cell carcinoma, Wilms tumor, and other small round blue cell neoplasms, highlighting the need for histopathological confirmation.

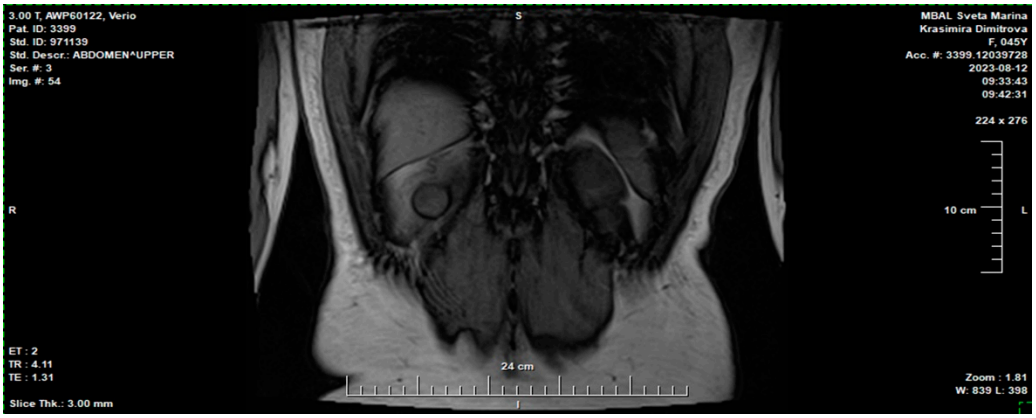

Figure 1. Axial T2-weighted MRI of the right kidney lesion, demonstrating a well-demarcated multicystic mass with septations and nodular thickening (scale bar shown).

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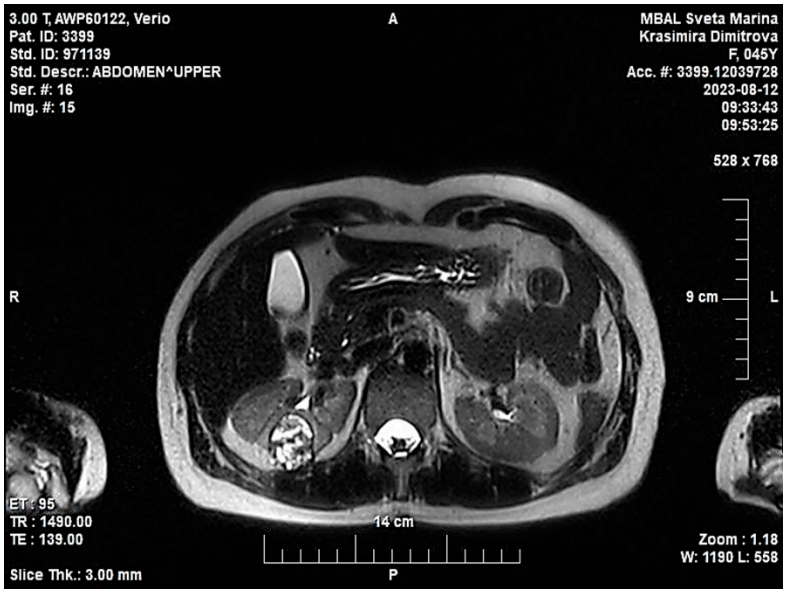

Figure 2. Coronal T2-weighted MRI showing dorsal protrusion of the right renal lesion with mixed signal intensity; septa are markedly hypointense.

2.3. Surgical Intervention

In October 2023, the patient was admitted to the Clinic of Urology, University Hospital "St. Marina," Varna, where partial resection of the renal tumor was performed.

2.4. Histopathology

The lesion was composed of monotonous small round cells with scant, clear cytoplasm and round-to-oval nuclei lacking prominent nucleoli. The cells formed solid nests and Homer-Wright rosettes. Scattered foci of necrosis and numerous apoptotic bodies were present. Mitotic activity was 5/10 high-power fields. PAS staining highlighted cytoplasmic glycogen granules (Figure 3).

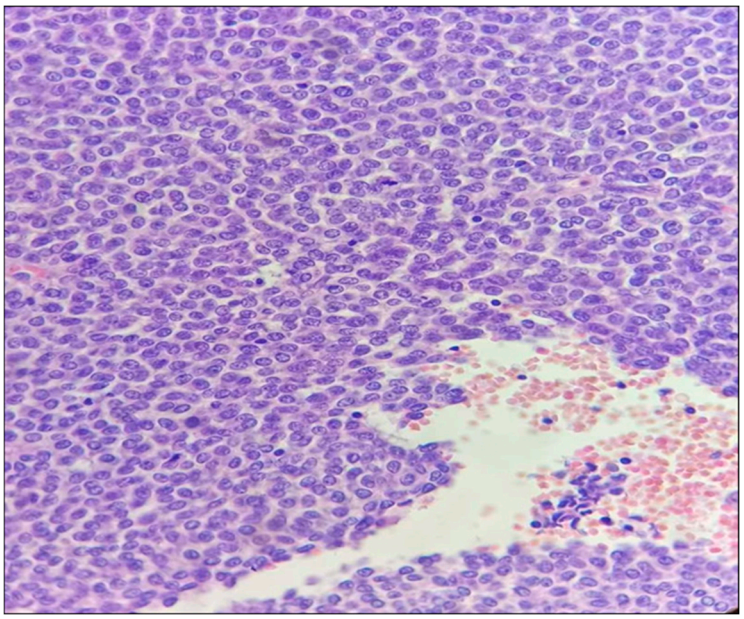

Figure 3. Histology (Hematoxylin and eosin, ×400) of the renal tumor: sheets of small round cells forming Homer-Wright rosettes; PAS staining highlights cytoplasmic glycogen granules.

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2.5. Immunohistochemistry

Immunophenotyping revealed positivity for CD99, Cyclin D1, WT1, vimentin, S100, p53 (~50%), and synaptophysin (~30%), and negativity for CD117, CD10, inhibin, CK7, GATA3, CD34, SMA, CK AE1/AE3, HMB45, and Melan-A. Ki-67 proliferation index was approximately 15%. The combination of morphological features and immunophenotype strongly supported a diagnosis of extraskeletal ES, pending molecular confirmation

2.6. Molecular Genetic Analysis

To confirm the diagnosis, molecular analysis was performed on formalin-fixed tumor tissue at an external reference laboratory (Eurofins Biomnis, Lyon, France). FISH analysis confirmed EWSR1 rearrangement in 100% of nuclei, establishing definitive diagnosis of primary renal ES and guiding subsequent multimodal therapy.

2.7. Differential Diagnosis

The differential diagnosis included other "small round blue cell" tumors, such as Wilms tumor, neuroblastoma, clear cell sarcoma of the kidney, and lymphoma. Integration of histological, immunohistochemical, and molecular findings established the final diagnosis of primary renal extraskeletal ES (Table 1).

Table 1. Diagnostic summary.

Feature	Result
Tumor size	28 × 23 × 27 mm
Histology	Small round blue cells, Homer-Wright rosettes
Immunohistochemistry	CD99+, Cyclin D1+, WT1+, vimentin+, S100+, Ki-67 ~15%
Molecular	EWSR1 rearrangement (FISH)

2.8. Treatment and Follow-up

Following diagnostic confirmation, the patient underwent right nephrectomy at a specialized center in Austria, followed by systemic chemotherapy according to the VDC/IE protocol (vincristine, doxorubicin, cyclophosphamide alternating with ifosfamide and etoposide). Given the history of breast carcinoma at age 37 and the subsequent diagnosis of a second malignancy at age 45, medical genetic counseling was provided to evaluate the possibility of Li-Fraumeni syndrome (germline tumor protein 53). The patient declined genetic testing. At 6-month follow-up, she remained disease-free. Surveillance was planned every 3 months for the first 2 years.

3. Discussion

Primary renal extraskeletal Ewing sarcoma is an extremely rare malignancy. Although early reports described fewer than 100 cases in the literature, more recent systematic reviews indicate that approximately 300–370 cases have been documented worldwide, with adult cases representing only a small fraction and typically reported as isolated case reports or small case series [18–20]. Clinical manifestations are frequently nonspecific, with patients most commonly presenting with flank pain, hematuria, or a palpable renal mass [21,22]. Such nonspecific clinical presentations may delay diagnosis, allowing the tumor to progress to advanced stages with early metastatic dissemination, most commonly to the lungs, lymph nodes, liver, and bone [23]. The combination of aggressive tumor biology and extreme rarity therefore poses substantial challenges for timely recognition and appropriate management.

Definitive diagnosis of renal ES requires an integrated diagnostic approach combining histopathology, immunohistochemistry, and molecular testing. As a member of the "small round

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blue cell tumor" family, ES shares morphological characteristics with several other pediatric and adult neoplasms, necessitating careful and systematic differential diagnosis. Critical entities to exclude include Wilms tumor, neuroblastoma, clear cell sarcoma of the kidney, desmoplastic small round cell tumor, lymphoma, small-cell osteosarcoma, and renal neuroendocrine tumors [24]. Characteristic histological findings, such as Homer–Wright rosettes and diffuse, strong membranous CD99 expression, represent important diagnostic clues. Nevertheless, these morphological hallmarks alone are insufficient for definitive classification because overlapping immunophenotypic and morphological features may occur among small round cell neoplasms. Molecular confirmation through detection of EWSR1–ETS gene rearrangements using FISH, RT-PCR, or next-generation sequencing remains the gold standard [25]. In the present case, the combination of classical morphology, immunohistochemical profile, and FISH-confirmed EWSR1 rearrangement established the definitive diagnosis, highlighting the indispensable role of integrated molecular diagnostics in adult renal ES.

Given the exceptional rarity of primary renal ES, no standardized site-specific treatment guidelines currently exist. Consequently, management strategies are largely extrapolated from therapeutic approaches established for osseous ES. A multimodal treatment strategy consisting of complete surgical resection combined with systemic chemotherapy is currently considered the cornerstone of management, achieving favorable outcomes in localized disease [21]. The most widely used chemotherapy regimen remains VDC/IE (vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide), which has demonstrated efficacy in both localized and metastatic disease [22]. Radiotherapy may also be considered in selected cases to enhance local control, particularly when complete surgical margins cannot be achieved. Nephron-sparing surgery may be considered in select patients with small, localized tumors, provided that complete resection is feasible and oncologic outcomes are not compromised [26,27]. This surgical approach may be particularly relevant in patients with preexisting renal impairment or a solitary kidney, where preservation of renal function is clinically important.

Although not yet part of standard clinical practice, emerging targeted therapeutic strategies are being actively investigated for ES. These include experimental EWSR1–FLI1 antagonists and novel immunotherapeutic approaches, such as chimeric antigen receptor T-cell therapy and immune checkpoint inhibitors. Preclinical studies have demonstrated that inhibition of EWSR1–FLI1 activity can suppress tumor proliferation and growth both in vitro and in vivo, while early-phase clinical trials are currently evaluating the safety and efficacy of immunotherapeutic approaches in patients with advanced disease [28–33]. These developments highlight the growing potential of molecularly guided and personalized therapeutic strategies, particularly for patients with high-risk, recurrent, or metastatic ES.

Renal ES is generally considered more aggressive than ES arising in bone or other soft tissue sites, with a greater propensity for early metastatic spread and local recurrence [34]. This aggressive behavior translates into a comparatively poorer prognosis than that observed in classic osseous ES, with survival largely dependent on tumor stage at presentation and the completeness of surgical resection. Data from broader ES cohorts emphasize high relapse rates and underscore the importance of vigilant long-term surveillance. Given the extreme rarity of primary renal ES, specific prognostic factors are not well defined. Prognostic insights are therefore typically extrapolated from osseous ES and include tumor size, presence of metastases at diagnosis, completeness of surgical resection, and molecular characteristics, particularly the EWSR1–FLI1 fusion type [12–17].

Finally, this case highlights the critical importance of interdisciplinary collaboration, encompassing urology, oncology, radiology, pathology, and molecular genetics, to optimize both diagnostic accuracy and therapeutic outcomes. Through coordinated multidisciplinary management and integration of advanced molecular diagnostics, clinicians can facilitate earlier recognition, accurate diagnosis, and more effective treatment of this rare and challenging malignancy.

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4. Conclusions

This case highlights an exceptionally rare instance of primary renal extraskeletal ES in an adult. Integrated diagnostic evaluation, including imaging, histopathology, immunohistochemistry, and molecular confirmation of EWSR1 rearrangement, was essential for establishing a definitive diagnosis. Surgical intervention followed by systemic chemotherapy according to the VDC/IE protocol provided effective disease control.

The case underscores the critical importance of early recognition, interdisciplinary collaboration, and personalized therapeutic strategies in managing rare adult renal ES. Clinicians should maintain a high index of suspicion for renal "small round blue cell" tumors and employ a multimodal, molecularly guided approach to optimize patient outcomes. This report contributes to the limited literature on renal ES and provides guidance for diagnosis, management, and surveillance of similar cases.

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Institutional Review Board Statement: The study was conducted in full compliance with the ethical principles set forth in the Declaration of Helsinki (1975, revised in 2013), as well as in accordance with the applicable national regulations governing research involving human subjects. The study received prior approval from the local Ethics Committee, as detailed below: Ethics Committee Name: Ethics Committee for Scientific Research, Medical University of Varna; Approval Code: Protocol/Decision No. 140; Approval Date: 01 February 2024.

Informed Consent Statement: Written informed consent was obtained from the patient for publication of this case report.

Data Availability Statement: No new datasets were generated or analyzed during the preparation of this case report.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

ES	Ewing sarcoma
EWSR1-FLI1	Ewing sarcoma breakpoint region 1—Friend leukemia virus integration 1
FISH	Fluorescence in situ hybridization
IE	Ifosfamide, etoposide
MRI	Magnetic resonance imaging
PAS	Periodic acid–Schiff
RT-PCR	Reverse transcription polymerase chain reaction
VDC	Vincristine, doxorubicin, cyclophosphamide

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