



Case Report

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Primary Renal Ewing Sarcoma: A Case Report and Review of the Literature

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Abstract

Primary Ewing sarcoma of the kidney is an extremely rare and aggressive tumor affecting young adults. We present the case of a 22-year-old male with primary Ewing sarcoma/primitive neuroectodermal tumor (EWS/PNET) of the kidney who underwent right radical nephrectomy and adjuvant chemo-radiation.

Keywords

Renal mass, Ewing's sarcoma, PNET

Introduction

The differential diagnosis of a renal mass in a young adult includes renal cell carcinoma, Wilms tumor, neuroblastoma, lymphoma, metastatic renal involvement from another primary sight, and, rarely, primary renal sarcoma [1,2]. The Ewing sarcoma family tumors (ESFT), which include Ewing sarcoma of bone, extraosseous Ewing sarcoma, and primitive neuroectodermal tumor (PNET), exhibit highly aggressive malignant behavior. Though Ewing sarcoma (ES) is the second most common malignancy of bone and soft tissue in children and young adults, primary extraosseous ES is quite rare [3]. Indeed, just over 100 reported cases of ES of the kidney has been reported worldwide since the first documented case by Seemayer, et al. in 1975 (Table 1) [1,4]. Here, we present a case of extra-osseous Ewing sarcoma/primitive neuroectodermal tumor (EWS/PNET) of the kidney.

Case Presentation

A 22-year-old male presented to the Emergency Department of a community medical center with abdominal pain for 1-2 weeks. He denied any hematuria, dysuria, flank pain, fevers, bone pain, anorexia, nausea, vomiting, or weight loss. His past medical history was negative for renal calculi or any

chronic illnesses. He endorsed occasional smoking, but denied any hazardous or environmental exposures through his work in construction. An initial evaluation with a non-contrast CT of the abdomen and pelvis revealed a 19 cm diffusely heterogeneous right renal mass. Further evaluation with an abdominal MRI confirmed the presence of a right renal mass, measuring 20.3 × 12.6 × 10.6 cm, with both solid and cystic components (Figure 1). A chest CT identified multiple sub-centimeter lung nodules. Initial laboratory testing was unremarkable with the exception of a mild leukocytosis and 2 + blood on urine dipstick.

Given this presentation and high suspicion for renal car-

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Table 1: Selected prior reports of primary Ewing sarcoma of the kidney with the site of metastasis and treatment modalities.

Study	Patient age, sex	Metastasis	Treatment
Moustafellos P, et al. [15]	32, M	No	Radical nephrectomy, Adjuvant chemotherapy
Fergany AF, et al. [16]	31, M	Yes - lung	Radical nephrectomy, Adjuvant chemotherapy
Lazzara B, et al. [17]	38, M	No	Radical nephrectomy, Neoadjuvant chemotherapy, Adjuvant chemotherapy, Radiation
Vrdoljak DV, et al. [18]	51, M	Yes - liver, Right iliac wing	Radical nephrectomy, Adjuvant chemotherapy
Almeida MFA, et al. [1]	19, M	Yes - lung	Radical nephrectomy, Adjuvant chemotherapy
Liu Z, et al. [19]	37, M	No	Radical nephrectomy, Adjuvant chemotherapy
Chakrabarti N, et al. [20]	24, F	Yes - lung	Radical nephrectomy, Adjuvant chemotherapy
Nam JK [21]	30, M	No	Radical nephrectomy, Adjuvant chemotherapy
Alasmari F, et al. [22]	15, F	Yes - lung	Radical nephrectomy, Adjuvant chemotherapy, Radiation

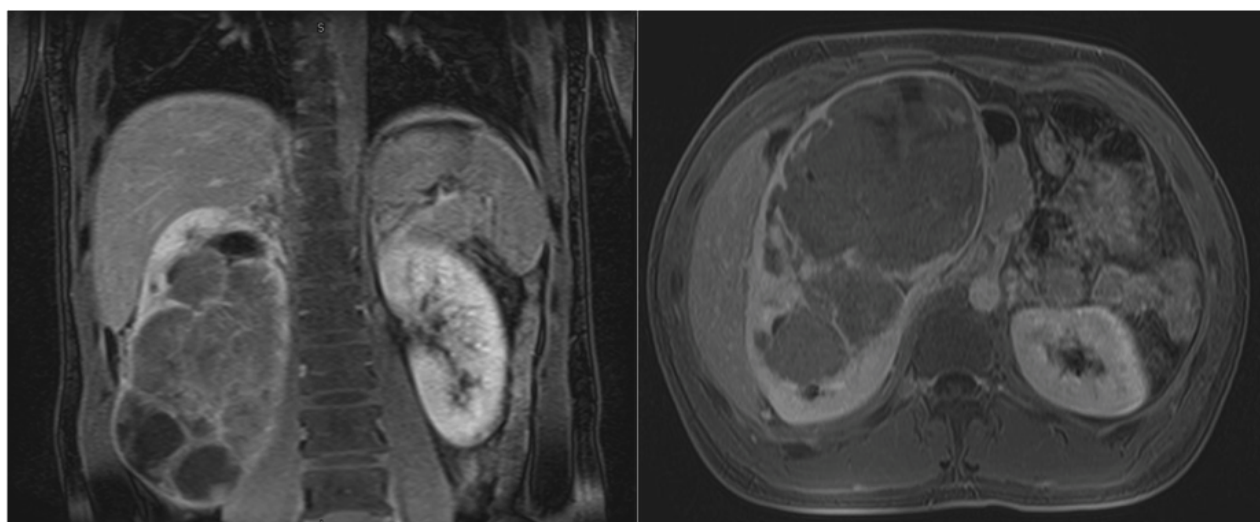


Figure 1: Representative MRI images showing the 20.3 × 12.6 × 10.6 cm, with both solid and cystic components.

cinoma, the patient was referred to a NCI-designated comprehensive cancer center for further evaluation and management of his large right renal mass. The patient was reviewed at our multidisciplinary tumor board and Pediatric Hematology/Oncology was asked to participate given the possibility of a Wilms tumor. He subsequently underwent a right open radical nephrectomy and was discharged on post-operative day 2.

Tumor pathology demonstrated an extraosseous Ewing sarcoma/primitive neuroectodermal tumor with evidence of lymphovascular invasion and microscopic positive tumor at the soft tissue surrounding the vascular margin (R1 resection). Immunohistochemical staining revealed the neoplastic cells positive for CD99 and FLI-1. Cytogenetics showed EWSR1 gene translocation involving the chromosome 22q12. The morphology, immuno-profile and chromosomal aberration support the diagnosis of PNET (Figure 2).

A PET/CT scan performed 2 weeks post-operatively showed residual FDG uptake in the area of the right kidney, but did not demonstrate any other significant hypermetabolic areas. The patient's subcentimeter lung nodules were

considered metastatic disease based on clinical staging. A bone marrow biopsy was negative for metastatic disease. The patient enrolled in a clinical trial (NCT02306161) evaluating adjuvant chemotherapy consisting of vincristine/adriamycin/cyclophosphamide alternated with ifosfamide/etoposide in combination with ganitumab for patients with metastatic Ewing sarcoma. He also received 50.4 Gy radiation therapy to the right flank in addition to whole lung irradiation (WLI) to 15 Gy in 10 fractions. In efforts to minimize any overlap between the flank radiation and WLI, as well as minimizing secondary effects of radiotherapy, he was treated with proton beam therapy (PBT) to the flank (Figure 3).

Discussion

Unlike in renal cell carcinoma, primary renal EWS/PNET is most often a disease of relatively younger patients. The mean age at diagnosis is just 30.4 years, and more than half of newly diagnosed cases are seen in males [5,6]. Common presenting symptoms are similar to that of other renal tumors, and no radiographic features have been identified which are indicative of the pathologic diagnosis [1,2]. Given its aggressive nature, patients typically present with advanced

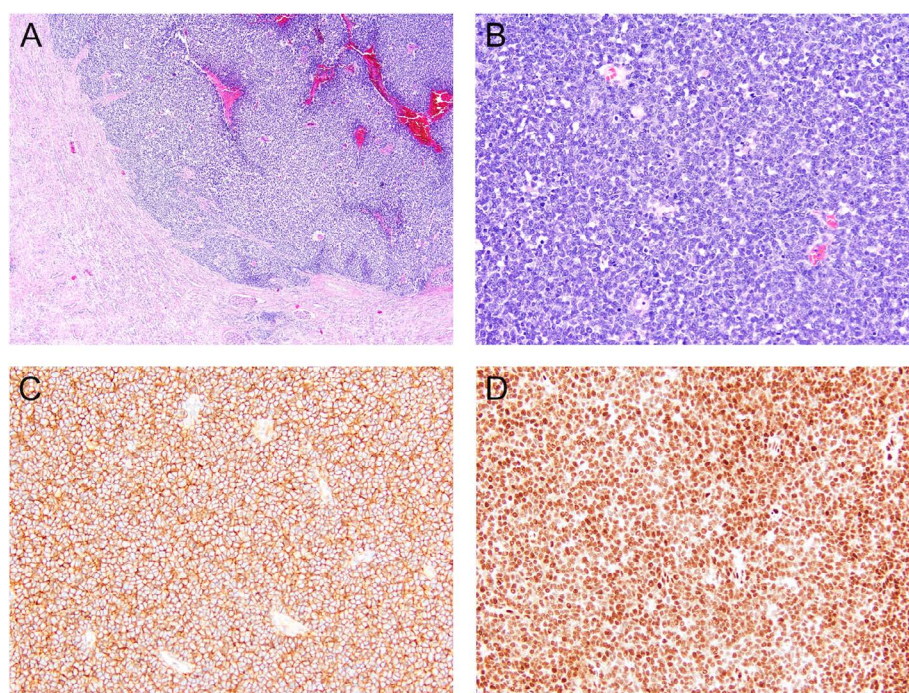


Figure 2: Sheets of monotonous small round blue cells with scant cytoplasm, hyperchromatic nuclei and inconspicuous nucleoli A) Under low magnification (20x) with adjacent renal parenchyma; B) Under higher magnification (200x). The tumor shows strong; C) Membrane staining for CD99 (200x); D) Nuclear staining for FLI-1 (200x).

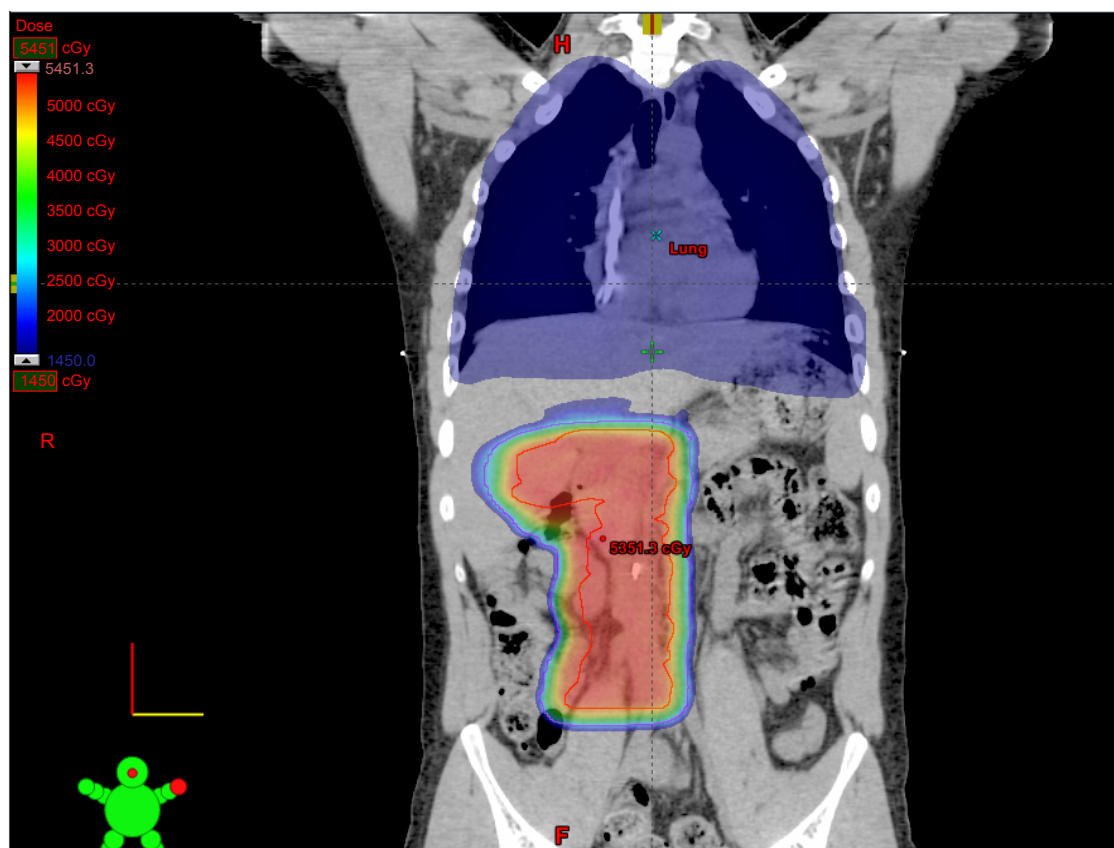


Figure 3: Proton Beam Therapy treatment fields to both the lungs and right flank area, including the resection bed.

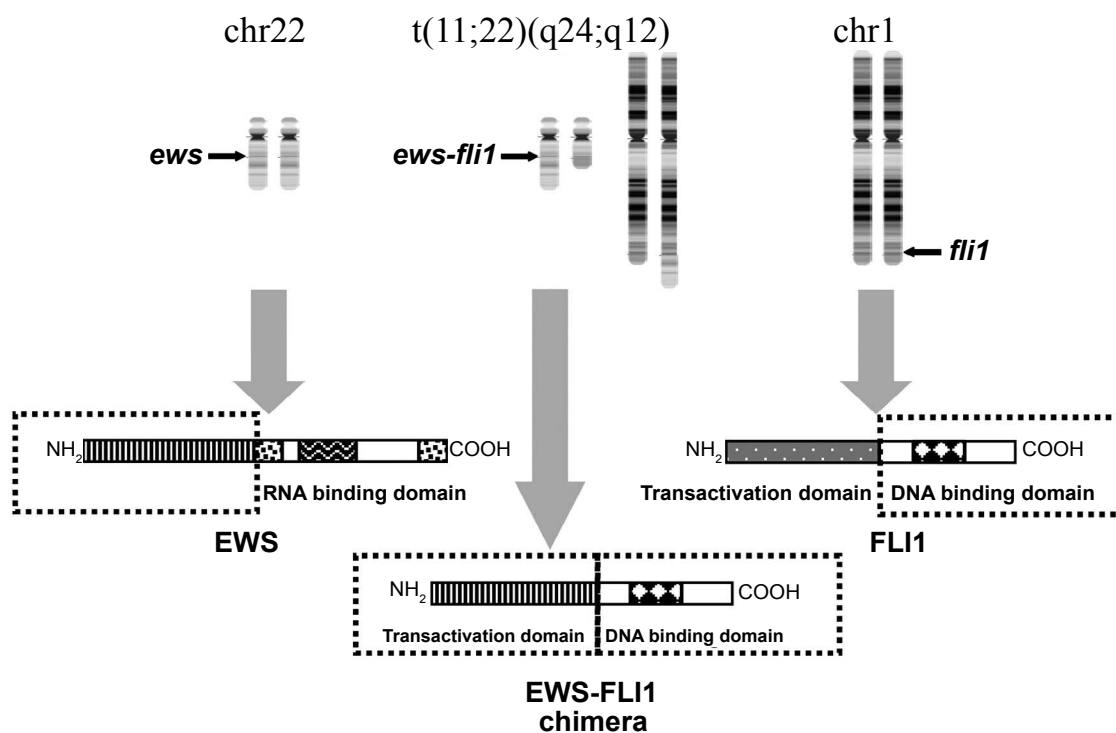


Figure 4: Reciprocal translocation of chromosomes 11 and 22 t(11;22) which results in the formation of an EWS-FLI1 fusion gene (Adapted with permission from Bernstein, et al. [10]).

disease and early metastasis [1]. Thus, early and accurate diagnosis of the disease is essential in determining prognosis and establishing a therapeutic strategy.

Immunohistochemistry and molecular studies are necessary in diagnosing Ewing sarcoma family of tumors (ESFT), as they aid in differentiating EWS from other tumors with histologic resemblance, such as Wilms tumor, neuroblastoma, rhabdomyosarcoma, and lymphoma. One typical histological feature of Ewing sarcoma includes vague rosette formations, and CD99 over expression is a non-specific finding present in nearly all ESFTs [2,7-9]. A more unique feature found in 70-90% of ESFTs is the DNA translocation t(11;22), which generates the EWS-FL1 fusion oncogene (Figure 4) [2,5,6,9,10]. Diagnosis in this patient was made via Fluorescence *in situ* Hybridization (FISH). At our institution, the break apart FISH is the standard method for diagnostic confirmation of Ewing sarcoma. This method has been shown to be more sensitive and specific compared to RT-PCR, as some cases that are positive by FISH may be negative by RT-PCR [11]. Therefore, we do not perform RT-PCR on cases already confirmed by FISH.

Common sites of metastasis include lung, liver, abdominal lymph nodes, and bone [6]. Prognosis is poor, with a 5-year survival of 60-70% in non-metastatic disease and 20-30% in metastatic disease [2,6]. For ESFT, neoadjuvant chemotherapy along with local control and adjuvant chemotherapy are usually performed [10]. Due to the rarity of primary renal EWS/PNET, a standardized treatment protocol has not been established, though these patients are generally treated with regimens for other ESFT. As such, the available literature does suggest a high response rate to chemotherapy, especially in local disease [5,6,12,13].

A study by Zollner, et al. [12] retrospectively analyzed a database of patients enrolled in clinical trials for Ewing's sarcoma over a 30 year period and found 24 patients with primary renal involvement. All patients were treated according to a chemotherapy protocol modeled after established osseous EWS treatments, which consisted of 6 cycles of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE), then risk-adjusted consolidation therapy following local control. The 3-year overall survival for all those examined was 0.80, while it was just 0.58 for metastatic disease.

After tumor board review, the patient described in this case was not treated with neoadjuvant therapy due to symptoms from mass effect. However, given the response of ESFT to neoadjuvant treatments, clinicians should have a high index of suspicion for this type of tumor pathology in younger patients with renal masses. While renal biopsies have been somewhat controversial, the benefit of obtaining a tissue diagnosis of renal EWS and starting neoadjuvant treatment may outweigh the risk of biopsy. Rowe, et al. examined an institutional series of 10 patients with renal EWS and showed that 7 of these patients did undergo a biopsy which led to chemotherapy prior to surgical resection [14-22].

Conclusions

Primary renal EWS/PNET is a rare yet aggressive tumor that affects mostly men in the second to third decade of life, making a high clinical index of suspicion important in this population. Immunohistochemistry is essential to diagnosis given its close histologic resemblance to other renal round cell tumors. Although overall prognosis is poor, early diagnosis and treatment by a multidisciplinary team with multimodal thera-

py can improve outcomes. Results of ongoing and future clinical trials are needed to optimize therapeutic pathways and therefore all providers are encouraged to discuss clinical trial participation with their patients.

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