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Case Presentation

Primary Renal Ewings Sarcoma/Primitive Neuroectodermal Tumor (PNET) Of The Kidney, Can It Be Diagnosed On Imaging? A Case Report

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Abstract

Primary renal Ewing Sarcoma/primitive Neuroectodermal Tumor (PNET) of the kidney represents a rare aggressive pathologic entity seen in children and young adults. Here we present a case of a 46 year old woman who presented with bilateral lower quadrant abdominal pain and microscopic hematuria. Radiologic imaging demonstrated a large heterogeneous, vascular mass involving the upper pole of right kidney causing diffuse enlargement of kidney on ultrasound. Further imaging with a CT scan showed a moderately enhancing, diffusely infiltrating right upper pole mass with a tumor thrombus in right renal vein that extended into the infrahepatic portion of the inferior vena cava. An ultrasound guided biopsy of the lesion demonstrated a mass composed of neoplastic cells with primitive histomorphologic features and expression of vimentin, CD99 (MIC2), FLI-1, and BCL-2. The tumor was negative for WT-1, pankeratin, synaptophysin, chromogranin and CD45. FISH analysis showed a rearrangement of EWSR1 in 89% of cells. The patient subsequently underwent a right nephrectomy, IVC thrombectomy and regional lymph node dissection. The imaging features of renal PNET can be uncharacteristic and this tumor is mainly diagnosed based on the combination of pathological and radiological findings. By presenting this case report we expect to further knowledge on the imaging features and various options for preoperative diagnosis of renal ES/PNET. Based on the case that we are presenting, we suggest diffuse infiltrative appearance of the tumor, moderate grade enhancement, peripheral areas of hemorrhage and necrosis and tumor thrombus in renal vein and IVC can suggest the imaging diagnosis of renal ES/PNET preoperatively.

Keywords: Renal Primitive Neuroectodermal Tumor (Rpnet); Renal Ewing Sarcoma (EWS); Computerized tomography; Sonography; Ultrasound

Introduction

Primary Ewing Sarcoma/Primitive Neuroectodermal Tumor of the kidney (ES/PNET) represents a rare group of small round cell tumor that is characterized by an aggressive clinical course. Historically, Ewing sarcoma and primitive neuroectodermal tumors were considered to be separate pathologic entities; however, molecular studies have established that these tumors are a part of the same tumor family and exhibit similar biologic behavior. As such, the term Ewing sarcoma now encompasses both entities [1]. ES/PNET tumors are most commonly identified in the axial skeleton, appendicular skeleton and central nervous system; however extracranial and extraosseous tumors have also been described [2]. ES/PNET lesions of the kidney are exceedingly rare and were first reported by Seemayer and colleagues in 1975 [3]. Subsequent cases in the literature have shown that this tumor tends to affect young adults (median age 28) with a slight male predominance. Patients usually remain asymptomatic until tumor reaches large size and usual presenting symptoms are flank and/or abdominal pain (85%), a palpable mass (60%) and hematuria (37%) [4]. Systemic symptoms such as weight loss (14.5%) and fever (9.7%) may occur and must be differentiated from infectious etiologies [5]. The prognosis of renal ES/PNET is generally poor, with a 5 year disease-free survival rate of 45-55% and an overall survival of 20% [5].

Here we present a case of primary renal ES/PNET in a 46 year old female and discuss the radiographic and morphologic features of this lesion.

Case Presentation

A 46 year old woman with a history of hypertension, hyperlipidemia and nephrolithiasis presented to the emergency room with a 2-3 week history of intermittent bilateral lower quadrant abdominal pain and nausea. Initial laboratory studies showed trace hematuria and 2+ proteinuria. An abdominal ultrasound was performed and showed a heterogenous vascular mass in the upper pole of right kidney with tumor thrombus extending into the right renal vein and Inferior Vena Cava (IVC) (Figure 1A,1B &1C). A staging contrast enhanced CT scan of the abdomen revealed a 15.7 cm lobulated, infiltrative mass in the upper pole of right kidney causing diffuse enlargement of the kidney with diffuse, moderate heterogenous enhancement following intravenous contrast administration. As seen on the ultrasound, the tumor showed extension into the right renal vein and IVC, ending just below the level of the hepatic veins (Figure 2A,2B,2C

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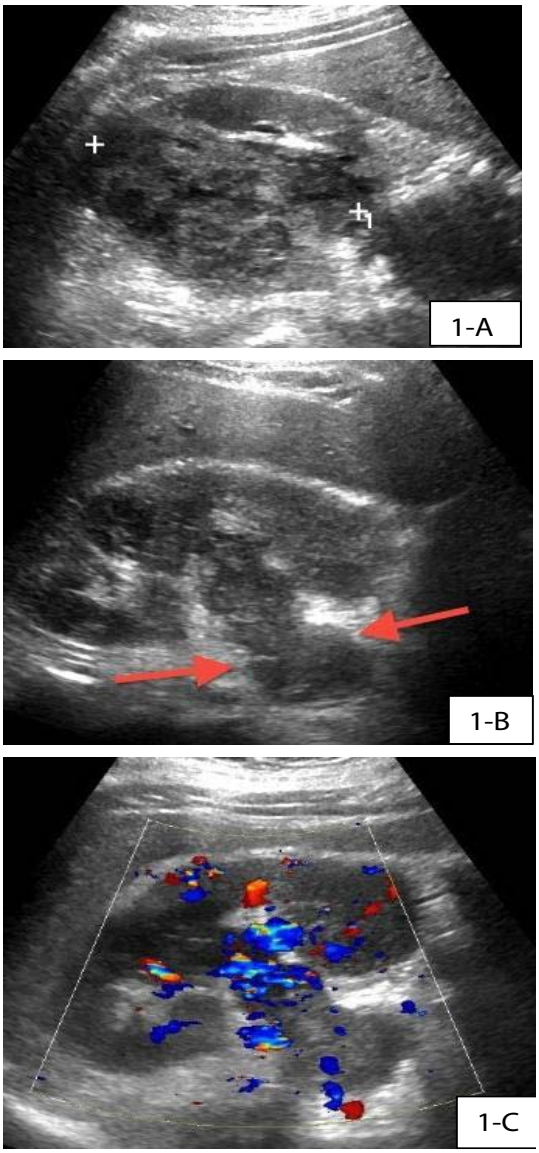

Figure 1: rPNET of the right kidney in a 46-year-old woman.
Ultrasound (**A, B)** and Doppler images (**C**), of right kidney demonstrate an ill-defined heterogenous is to hypoechoic mass showing moderate vascularity in the upper pole with extension of the tumor into the renal pelvis (red arrows). Please note that the contour and shape of the kidneys is well maintained.

& 2D). Despite the large size of the mass, the contour of the kidney was well maintained. The mass showed a few hypoenhancing areas, likely representing hemorrhage and necrosis. There was no evidence of metastatic disease at the time of initial presentation. Based on these imaging features, a diagnosis of renal cell carcinoma with tumor thrombus extending into renal vein and IVC was rendered.

A core biopsy of the mass was performed under ultrasound guidance and demonstrated a mass composed of primitive, monomorphic small round blue cells arranged in a sheet like growth pattern with round nuclei, fine chromatin, scant eosinophilic cytoplasm and indistinct cell boards (Figure 4A). Immunohistochemical studies demonstrated that the neoplastic cells were positive for vimentin, CD99 (MIC2), FLI-1 and BCL-2 (Figure 4B, 4C). The neoplastic cells were negative for pankeratin, synaptophysin, chromogranin, EMA, WT-1, CD45, CD3, CD20 and myogenin. Fluorescence In Situ Hybridization (FISH) analysis of the EWSR1 locus on chromosome 22q12 was performed using DNA probe EWSR1 BAP and demonstrated a rearrangement signal pattern in 89% of the tumor nuclei. Based on the morphologic, Immunohistochemical and cytogenetic findings, a diagnosis of primary renal ES/PNET was established.

The patient subsequently underwent four cycles of neoadjuvant chemotherapy with Vincristine, Actinomycin-D and Cyclophosphamide (VAC) alternating with Ifosfamide and Etoposide (IE). With no additional tumor growth, a right nephrectomy, IVC thrombectomy and regional lymph node dissection was performed. Gross examination of the kidney revealed a 15.7 x 7.6 x 5.2 cm pink-tan, fleshy, infiltrative mass with focal areas of hemorrhage and necrosis (comprising approximately 20% of the lesion). The tumor grossly invaded the sinus fat and renal vein (Figure 3). The final pathological tumor staging was defined as T2b (more than 5 cm in greatest dimension, deep tumor) and N0 (no nodal metastasis).

Following nephrectomy, additional chemotherapy with VAC/IE was initiated as well as a course of radiation therapy. Patient had tumor recurrence approximately 22 months following her initial diagnosis after which she passed away.

Discussion

Due to the poor prognosis of primary renal ES/PNET, accurate and timely diagnosis plays a significant role in proper patient management. Whether the tumor is accompanied by classic symptoms or is asymptomatic, the lesion is often first detected and characterized by radiographic imaging. The imaging characteristics of this neoplasm are often non-specific and demonstrate significant overlap with other renal tumors, including renal cell carcinoma, Wilms tumor, neuroblastoma, lymphoma, desmoplastic small round cell tumor, renal sarcomas and metastatic carcinoma [6]. On ultrasound, renal ES/PNET may appear hypoechoic, isoechoic and/or hyperechoic to the adjacent renal parenchyma and show increased vascularity on Doppler imaging. Computed Tomography (CT) studies often demonstrate large, heterogenous masses that may or may not contain areas of hemorrhage or necrosis manifesting as homogenous or heterogenous areas of enhancement with diffuse calcifications. Areas of hemorrhage typically appear hyperdense while areas of necrosis appear hypodense on non-enhanced CT images [7]. On MRI, the tumor masses can appear lobulated with an isointense and/or hypointense appearance on T1-weighted images with a heterogeneous to hyperintense appearance on T2- weighted images. On gadolinium enhanced T1- weighted images, the tumors are characterized by heterogenous enhancement depending on the amount of necrotic tissue present [4,7]. Compared to other renal tumors with similar imaging characteristics, the areas of necrosis and hemorrhage seen in renal ES/PNET are more commonly located along the periphery of the tumor mass [8].

In this case, there was diffuse, infiltrative involvement of the kidney which differs from well-circumscribed, exophytic, often lobulated masses identified in renal cell carcinoma. Aside from ES/PNET, other tumors in the differential of an infiltrative mass include involvement by lymphoma [9], urothelial carcinoma, medullary

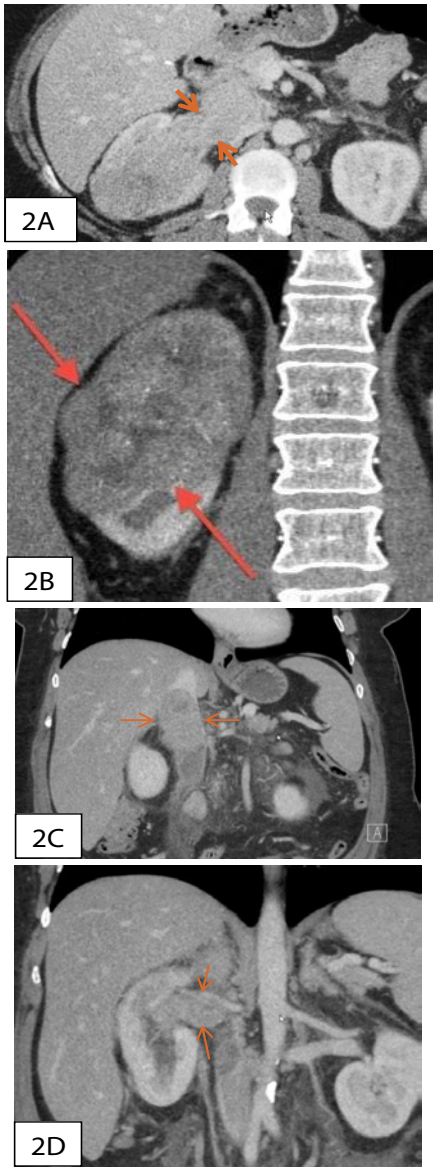

Figure 2: rPNET arising from the right kidney in a 46-year-old woman. Contrast enhanced axial (2**A**) and coronal (2B, 2C & 2D) CT images demonstrate a large diffusely infiltrating mass in upper pole of right kidney replacing the normal renal parenchyma showing moderate grade enhancement. Please note that the shape and contour of the kidney is well maintained and the mass is diffusely infiltrating. The mass is extending into the IVC and right renal vein which are expanded and completely filled with enhancing tumor thrombus (red arrows).

carcinoma and granulocytic sarcoma/leukemia [10]. The additional findings of tumor thrombus formation and peripheral areas of hemorrhage and necrosis also lend support to a diagnosis of ES/PNET rather than other renal tumors. Proper staging of renal ES/PNET is critically important. Indeed, Hyun Lee and colleagues showed that renal ES/PNETs had a more aggressive clinical course relative to conventional renal cell carcinoma and had a higher rate of renal vein thrombosis (80%) and distant metastasis at the time of initial diagnosis [6,11]. Common sites of metastasis include the lung, liver, and bone (25%–50%) [4]. Imaging techniques such as MRI and CT provide excellent evaluation of renal vein and IVC involvement as well as assessing for metastatic disease. Additionally, 99-technetium scintigraphy may be useful for the detection of bone metastases [4].

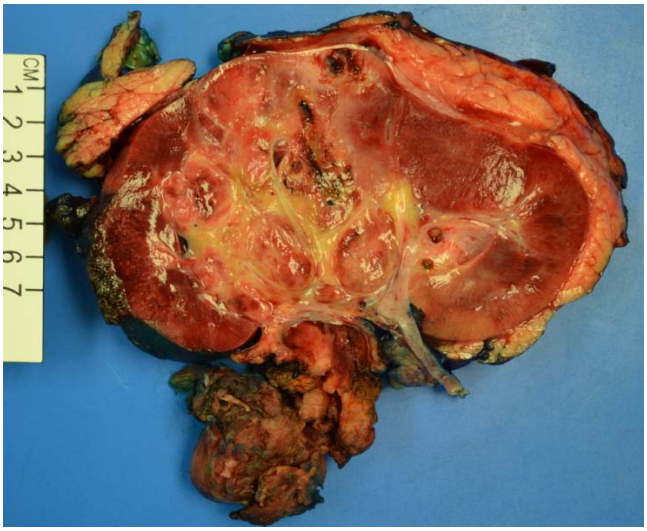

Figure 3: Gross morphological appearance of the resected tumor demonstrates a fleshy, infiltrative mass lesion with invasion of sinus fat and focal areas of hemorrhage and necrosis (comprising approximately 20% of the lesion).

Given the challenge of differentiating renal ES/PNET from other renal tumors on imaging, the diagnosis of these tumors is often predicated on an accurate surgical pathologic evaluation either on biopsy material or resected specimens [5]. Paralleling the challenges seen in radiology, the histopathologic features of renal ES/PNET demonstrate significant overlap with other small round blue cell tumors, including Wilms tumor, neuroblastoma, desmoplastic small round cell tumor and lymphoma. Immunohistochemical and molecular studies, therefore, play a critical role in differentiating these tumor types. Renal ES/PNET tumors are characterized by positive Immunohistochemical staining for CD99 (MIC2), FLI-1, vimentin and NSE and are typically negative for pankeratin, desmin, WT-1, GFAP and PAX2. The Immunohistochemical findings are further supported by the identification of a characteristic EWSR1/FLI1 fusion product that results from a t (11;22) (q24/q22;q12) translocation. This translocation is identified 90% of cases, and unequivocally confirms the diagnosis [12].

Once the diagnosis has been made, treatment strategies for renal ES/PNET include surgery, chemotherapy and radiation [4]. Surgical options include partial or total nephrectomy with cavotomy in cases of renal vein involvement [4,12]. Because the definitive diagnosis of renal ES/PNET often occurs postoperatively based on examination of resected tissue, multiagent chemotherapy is typically delivered adjuvantly [12]. Due to the rarity of this tumor in the kidney, treatment options are often based on therapies established for ES/PNET in other primary sites. Current studies suggest that the addition of ifosfamide and etoposide to a regimen containing doxorubicin, vincristine, dactinomycin, and cyclophosphamide, improves the outcome for patients with both non metastatic and metastatic disease [13]. Despite aggressive therapy, however, the prognosis for this tumor is poor, with a 20% as overall cure rate [14].

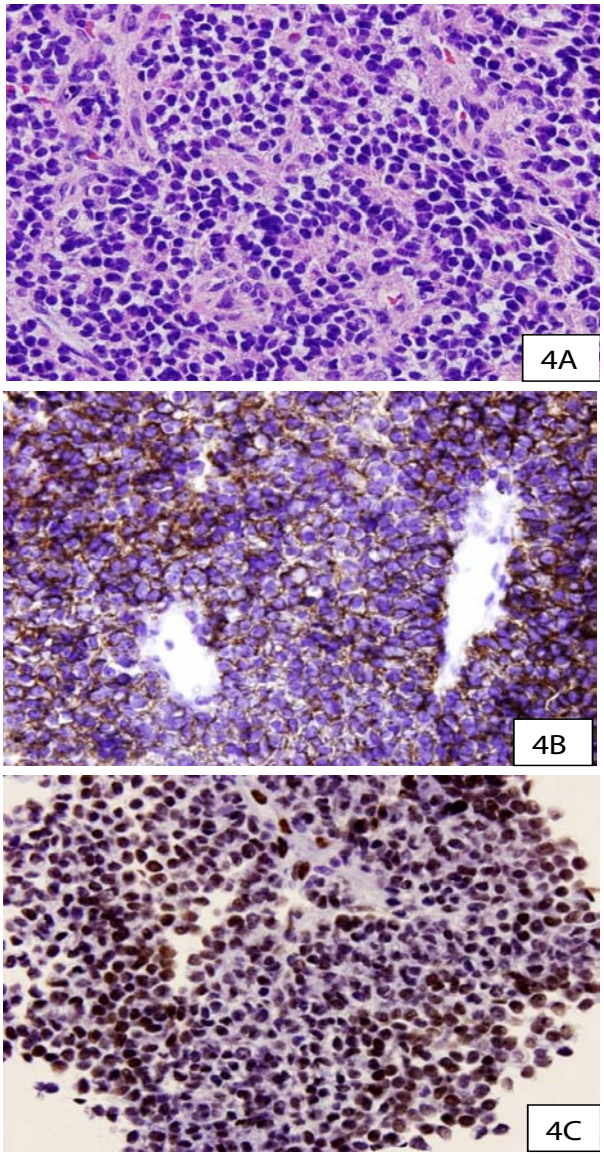

Figure 4: (4A) Hematoxylin and eosin stain demonstrates a malignant, monotonous population of small round blue cells (original magnification 600x). (4B) Strong membranous expression of CD99 (MIC2) (original magnification 600x) (4C) Nuclear expression of FLI-1 (original magnification 600x).

Conclusion

Renal ES/PNET is an extremely rare tumor characterized by a high rate of recurrence and an overall poor prognosis. Cross sectional imaging is vital in assessing resectability and identifying local and distant spread of disease. Although the imaging signs of this tumor are often nonspecific, the constellation of findings such as a large diffusely infiltrating renal mass showing moderate grade enhancement, peripheral areas of hemorrhage and necrosis and a tumor thrombus in the renal vein and IVC can preoperatively suggest a diagnosis of renal ES/PNET. Pathologic examination with Immunohistochemical and molecular studies are essential to make a definitive diagnosis and direct appropriate therapy. The aggressive nature of this tumor and poor prognostic rates make proper diagnosis and adequate treatment in expedited time invaluable.

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