

# Primitive Neuroectodermal Tumor of the Kidney with Renal Failure

Aharon Gefen MD MSc<sup>1,5</sup>, Myriam Weyl Ben Arush MD<sup>1,5</sup>, Israel Eisenstein MD<sup>2</sup>, Eugene Vlodavsky MD<sup>3</sup>, Roxolyana Abdah-Bortnyak MD<sup>4</sup> and Sergey Postovsky MD<sup>1,5</sup>

<sup>1</sup>Department of Pediatric Hematology Oncology and <sup>2</sup>Division of Pediatric Nephrology, Meyer Children's Hospital, Rambam Health Care Campus, Haifa, Israel

<sup>3</sup>Division of Oncology and <sup>4</sup>Pathology Institute, Rambam Health Care Campus, Haifa, Israel

<sup>5</sup>Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

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The peripheral primitive neuroectodermal tumor of the kidney belongs to the Ewing sarcoma family of tumors. A rare and highly aggressive malignant neoplasm, it usually affects young adults but a few pediatric cases have also been reported [1,2]. We present the case of a pediatric patient with renal PNET that had some special features, such as vena caval and right atrial thrombus and renal failure.

## PATIENT DESCRIPTION

A 16 year old girl with an unremarkable medical background except for menometrorrhagia and anemia treated with oral contraception presented with a history of right low back pain of one year's duration and a recent self-palpable right abdominal mass. Her physical examination was normal except for the mass. Initial laboratory tests were within normal limits, including renal function tests (blood urea nitrogen and creatinine). Abdominal ultrasonography, computerized tomography scan and echocardiography revealed a huge right renal mass

PNET = primitive neuroectodermal tumor

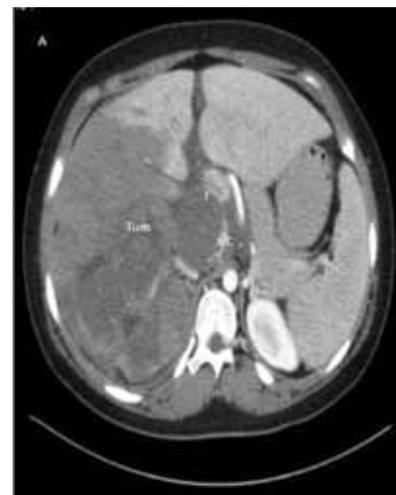
(21 x 14.4 x 11 cm) with a right renal vein, inferior vena caval and right atrial thrombus, and retroperitoneal lymphadenopathy [Figure A]. Evaluation for lung, bone and bone marrow metastasis was negative on CT scan, bone scintigraphy and bone marrow biopsy.

A tru-cut biopsy from the abdominal mass was performed. Histological examination revealed a small round cell tumor with strong positivity for CD99 and the presence of (11:22) translocation by polymerase chain reaction for EWS/FLI1 product. Staining for WT1, desmin, cytokeratin, Tdt and CD56 were all negative. The (11:22) translocation was absent in peripheral blood and bone marrow specimens. Accordingly, renal neuroectodermal tumor was diagnosed.

Treatment was started with neoadjuvant chemotherapy according to the EURO EWING 99 induction VIDE protocol, namely intravenous vincristine 1 mg/m<sup>2</sup>, ifosfamide 3000 mg/m<sup>2</sup>, doxorubicin 20 mg/m<sup>2</sup> and etoposide 150 mg/m<sup>2</sup> for 3 days. Because of the lack of ultrasound evidence of any positive response to the given chemotherapy and the potential danger posed by a persistent right atrial tumor thrombus, it was decided after the first course of chemotherapy to proceed to definitive surgery before completion of the originally planned neoadjuvant chemotherapy.

Radical nephrectomy and thrombectomy with implantation of inferior vena caval graft was undertaken.

**[A]** Computed tomography scan of abdomen showing a right renal tumor (Tum) with a tumor thrombus (T) extending into the inferior vena cava (IVC)



Postoperatively the patient received three additional induction cycles of chemotherapy 3 weeks apart. Because of her decreased renal function, the treatment was modified according to the following protocol: ifosfamide was omitted and replaced by intravenous cyclophosphamide 1500 mg/m<sup>2</sup>, and the dose of etoposide was reduced to 100 mg/m<sup>2</sup>. A EURO EWING 99 consolidation protocol cycle with intravenous vincristine 1 mg/m<sup>2</sup> and cyclophosphamide 1500 mg/m<sup>2</sup> was given thereafter (intravenous dactinomycin was omitted due to concurrent radiotherapy). The original chemotherapeutic plan (six induction cycles and seven subsequent consolidation cycles) was

changed considerably and ultimately abrogated due to persistent refractory thrombocytopenia that necessitated repeated platelet perfusions.

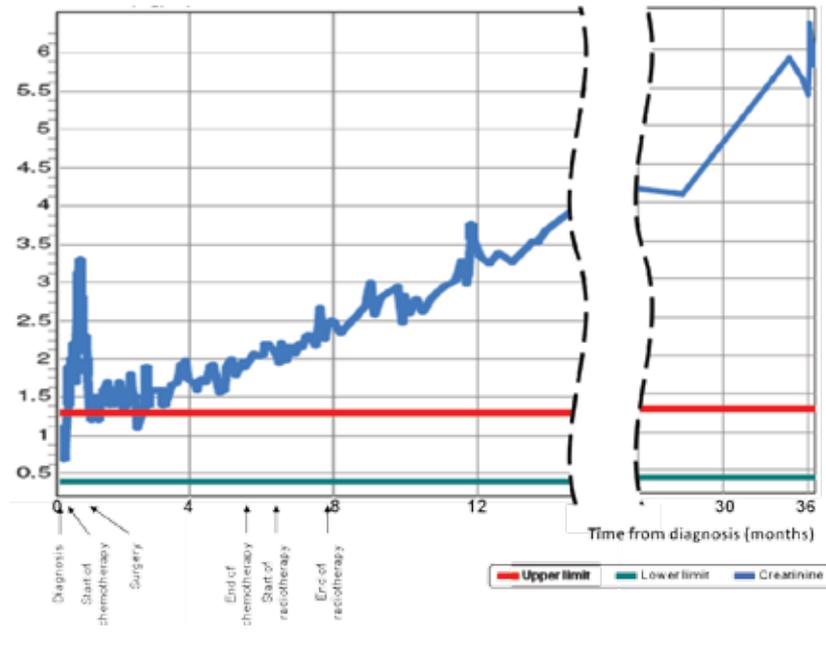
She completed her local control treatment with three-dimensional conformal radiotherapy to the tumor bed with a total dose of 45 Gy total, given at the end of the chemotherapy. She also received anti-thrombotic therapy with intravenous heparin followed by subcutaneous low molecular weight heparin 1 mg/kg/day (intermittently, according to platelet count) for 7 months.

During the first chemotherapy cycle the patient developed non-oliguric renal failure with creatinine levels rising from 0.9 mg/dl (normal initial BUN value, calculated glomerular filtration rate 97.6 ml/min/1.73 m<sup>2</sup>) to 3.3 mg/dl with measured GFR of 33 ml/min/1.73 m<sup>2</sup>. It should be noted that immediately after the first chemotherapy cycle she had been treated with vancomycin 12 mg/kg/dose twice daily, amikacin 12 mg/kg/dose once daily and furosemide 0.5 mg/kg/dose twice daily for 2 days. She had normal anion gap metabolic acidosis, most probably demonstrating renal tubular acidosis, which was treated with oral bicarbonate. Repeated renal ultrasound and Doppler scans were normal. Elevated blood pressure values of 150/100 mmHg emerged 15 months later, with good response to oral amlodipine. Now, 36 months after the diagnosis of rPNET, she feels well and has no clinical or radiographic evidence of recurrence but does have gradually deteriorating chronic kidney disease. She recently reached end-stage renal disease (creatinine 5.6 mg/dl with measured GFR of 10 ml/min/1.73 m<sup>2</sup>) [Figure B] and was referred to peritoneal dialysis.

During follow-up 3 months after completion of therapy, the patient developed mild pancytopenia (white blood cells 1.5 x 10<sup>9</sup>/L, neutrophils 1000 x 10<sup>9</sup>, platelets 29 x 10<sup>9</sup>/L, hemoglobin 8 g/dl).

BUN = blood urea nitrogen  
GFR = glomerular filtration rate  
rPNET = renal PNET

**[B]** Creatinine levels along the diagnosis, different stages of therapy (arrows) and follow-up. Notice the short abrupt acute renal failure just after start of chemotherapy, which gradually evolved into chronic kidney disease



Bone marrow examination was normal without morphological or cytogenetic evidence of a myelodysplastic syndrome or malignancy. Three months later, the pancytopenia resolved spontaneously.

**COMMENT**

The most common renal neoplasm in childhood is Wilms tumor, accounting for more than 90% of cases. Pediatric non-Wilms renal tumors, such as rPNETs and clear cell sarcomas, are generally more aggressive and associated with a poorer prognosis. rPNET is one form of the rare extraosseous Ewing sarcoma malignancies. It typically arises during childhood, adolescence or young adulthood. Differentiation from other small round cell tumors has prognostic and therapeutic implications. Presentation is similar to other renal tumors; the classic triad of abdominal pain, palpable mass and hematuria is the most common manifestation (84%, 60% and 38%, respectively), with fever and weight loss

being infrequent symptoms [1]. No specific signs have been described on ultrasound, CT scan or magnetic resonance imaging [1]. The diagnosis is based on histopathology supported by immunohistochemistry and specific chimeric transcripts. Strong membranous CD99 positivity is an almost universal feature of PNET. Approximately 90% of Ewing sarcoma/PNETs contain an EWS/FLI-1 fusion transcript that corresponds with the 11;22 translocation; other cases may be diagnosed on the basis of detection of other EWS-associated transcripts [2].

The prognosis of rPNET appears to be worse than the osseous equivalent Ewing sarcoma tumors, despite multimodal therapeutic approaches. In most studies the 5 year disease-free survival rate is 45–55% and the median relapse-free survival only 2 years for cases with advanced disease at presentation [1,2], although even worse figures have been presented – overall 1 and 2 year survival rates of 37.5% and 18.75%, respectively [3]. Ellinger et al. [1] collected data on

52 patients from small series and case reports, 30% of whom were younger than 20 years old. Most had metastasis at the time of diagnosis. The 5 year disease-free survival for patients with localized rPNET was 78%, but those with metastatic disease had a 2 year survival of around 20% [1]. Thyavihally et al. [2] reviewed their single-institute experience of 16 patients (median age 27 years, no data on the percentage of pediatric patients), 63% of whom had localized disease. The overall median survival was 40 months with a 3 year survival of 60% and a 5 year survival of 42% [2].

Several rPNET cases have been reported with a direct-extended tumor thrombus to the renal vein, IVC, right atrium or right ventricle, like our patient [3]. The presence of such a thrombus can be discovered preoperatively by imaging and requires special clinical and operational considerations. The frequency of a direct-extended tumor thrombus in pediatric reports is around 20–30% [3]. In the mixed pediatric and young adult population studied by Ellinger et al. [1], the numbers are similar – one-third of the 52 patients had a venous or cardiac extra-tumor thrombus extension, as compared to only one patient of 16 in the single-institutional review of Thyavihally et al. [2]. Two pediatric cases (both 17 years old) have been described with involvement of the hepatic veins and a clinical picture of Budd-Chiari syndrome; one died of hepatic failure [3,4].

When comparing pediatric patients with Wilms tumor, the incidence of tumor thrombus reaching cardiac compartments in patients with rPNET is notably higher. Thus, based on the

IVC = inferior vena cava

combined experience of the SIOP93-01/GPOH study and the SIOP2001/GPOH study, Szavay and colleagues [5] found only 33 of 1151 (2.8%) Wilms tumor patients with a tumor thrombus extending into the IVC or RA [5]. The reason for such a high incidence of vascular involvement seen in rPNET is unclear but may partly be explained by the very aggressive nature of PNET. Another explanation may be the anatomic proximity of rPNET tumors to the renal hilum and vessels.

Our patient developed chronic renal failure and renal tubulopathy early in the course of her treatment. This can be explained by the nephrotoxic chemotherapy treatment, particularly ifosfamide, in the setup of a single kidney, and as mentioned above, with concurrent delivery of other potentially nephrotoxic drugs. There is no evidence for pre-renal azotemia due to dehydration (normal initial BUN) or post-renal component of obstruction, as an explanation of the renal function insult. We cannot exclude a pretreatment subclinical renal injury due to the renal and IVC venous thrombus. To the best of our knowledge, renal insufficiency in association with rPNET has been reported previously in only two patients (aged 17 and 39 years), both of whom presented with abnormal creatinine levels [1,4]. There is no reference to the current renal status of the younger patient; the older one had a temporary partial improvement of renal function but eventually developed chronic renal failure and required dialysis. To the best of our knowledge our patient is the first to be reported with chronic renal failure clearly attributable to the disease and interventions.

The presence of decreased renal function further complicates the man-

agement of these high risk patients. It raises unanswered questions about the use of potentially nephrotoxic chemotherapeutic agents during treatment and contrast media agents in the follow-up of these patients who have a high potential for recurrence. Options like substitution of other drugs or reduced doses of potentially nephrotoxic drugs, or the use of alternative imaging methods (like ultrasonography, CT scan without contrast media or magnetic resonance imaging) for follow-up need to be discussed further. Presently, the wide use of PET-FDG coupled with high resolution CT scans may provide a satisfactory substitution for a CT scan with double contrast for follow-up during and after therapy.

#### Corresponding author:

**Dr. A. Gefen**

Dept. of Pediatric Hematology Oncology, Meyer Children's Hospital, Rambam Health Care Campus, P.O. Box 9602, Haifa 31096 Israel

**Phone:** (972-4) 854-2502

**Fax:** (972-4) 854-2007

**email:** r\_gefen@rambam.health.gov.il

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Since my house burned down  
I now own a better view  
of the rising moon

Mizuta Masahide (1657-1723), Japanese poet and samurai