Primary Primitive Neuroectodermal Tumor of the Urinary Tract

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Primary primitive neuroectodermal tumor (PNET) of the urinary tract is a rare disease with aggressive behavior and poor prognosis. We analyzed 851 cases of urinary tract malignancies in our hospital between 1984 and 2004. Only three (0.035%) cases with PNET of the urinary tract were identified. Presenting symptoms included flank pain and hematuria. The first case was a 44-year-old man with left renal PNET who underwent hand-assisted laparoscopic radical nephrectomy and adjuvant chemotherapy. There was no recurrent tumor at the 4-year follow-up. The second case was a 75-year-old woman with right renal PNET with inferior vena cava (IVC) thrombosis extending to the right atrium. The patient underwent right radical nephroureterectomy and IVC thrombectomy with cardiopulmonary bypass. She died of metastatic disease 7 months later. The third case was a 45-year-old man with left ureteral PNET. Left ureteral segmental resection and partial cystectomy were performed. Tumor recurrence was noted 7 years later. The patient died of disseminated disease 1 year after the discovery of recurrence. Urinary tract PNET appears to be an aggressive malignancy. Long-term survival is possible if complete resection is performed at an early stage. [J Formos Med Assoc 2006;105(12):1008–1012]

Key Words: immunohistochemical staining, primitive neuroectodermal tumor, urinary tract

Peripheral primitive neuroectodermal tumor (PNET) was first reported by Stout in 1918, who presumed the condition to be of neuroectodermal origin, most often presenting as a bone or soft tissue mass in adolescents and young adults.¹ Primary PNET arising from the urinary tract is rare, with only sporadic case reports. Here, we report two cases of primary renal PNET and one case of primary ureteral PNET.

Case Reports

The clinical courses, imaging studies, histologic features, and outcomes of the three patients are summarized in the Table.

Case 1

This 44-year-old male presented with gross hematuria and left flank pain of 2 months’ duration. Physical examination and laboratory tests were unremarkable. Computed tomography (CT) showed a heterogeneously enhanced left renal mass (9 cm in diameter) (Figure A). Bone scan and chest X-ray revealed no evidence of metastasis. Laparoscopic radical nephrectomy was performed. Grossly, the tumor was well demarcated and showed brown and yellow cut surfaces with focal hemorrhage and necrosis. Microscopic examination showed blue round tumor cells with occasional Homer-Wright rosette formation (Figure B). Immunohistochemical staining demonstrated that the tumor cells were positive for CD99 (1:120,
**Table.** Clinical and immunohistochemical (IHC) staining data in the three cases

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Location</th>
<th>Presentation</th>
<th>Treatment</th>
<th>Recurrence or metastasis</th>
<th>Survival (mo)</th>
<th>Status</th>
<th>Positive IHC staining</th>
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<tbody>
<tr>
<td>1</td>
<td>44</td>
<td>M</td>
<td>Lt kidney</td>
<td>Flank pain, hematuria</td>
<td>Surgery, chemotherapy</td>
<td>No</td>
<td>48</td>
<td>No evidence of disease</td>
<td>CD99, FLI-1</td>
</tr>
<tr>
<td>2</td>
<td>75</td>
<td>F</td>
<td>Rt kidney</td>
<td>Flank pain, hematuria</td>
<td>Surgery, chemotherapy</td>
<td>Local recurrence in liver, lung</td>
<td>7</td>
<td>Died of disseminated metastasis</td>
<td>NSE, S-100, vimentin, FLI-1, CD99</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>M</td>
<td>Lt ureter</td>
<td>Painless hematuria</td>
<td>Surgery, chemotherapy, palliative RT</td>
<td>Local recurrence in lung</td>
<td>24</td>
<td>Died of disseminated metastasis</td>
<td>CD99, FLI-1</td>
</tr>
</tbody>
</table>

*Lt = left; Rt = right; RT = radiotherapy; NSE = neuron-specific enolase.*

**Figure.** (A) Computed tomography shows a left renal mass (9 cm) at the middle and lower portions of the left kidney with central cystic components (arrow). (B) Monotonous small round blue cells with Homer-Wright rosette formation (arrow) (hematoxylin and eosin, 400x). (C) CD99 immunohistochemical stain shows positive membranous stain on tumor cell cytoplasmic surfaces (ABC method, 400x). (D) Positive nuclear FLI-1 immunohistochemical stain (ABC method, 400x).

monoclonal; Dako, Carpinteria, CA, USA) and FLI-1 (1:200, polyclonal; Santa Cruz Biotechnology, Santa Cruz, CA, USA) (Figures C, D), and negative for actin and cytokeratin. Adjuvant chemotherapy was given with VAC (vincristine 0.67 mg/day; adriamycin 25 mg/m²/day; cyclophosphamide 1200 mg/m²/day; and mesna for 3 days) for four courses, and IE (etoposide...
100 mg/m²/day; ifosfamide 1800 mg/m²/day for 5 days) for three courses. The patient had no evidence of recurrence at the 4-year follow-up.

Case 2
A 75-year-old female presented with right flank pain of 2 weeks’ duration. Physical examination revealed a palpable mass at the right upper abdominal quadrant. Laboratory data showed only anemia (hemoglobin, 9.1 g/dL). Magnetic resonance imaging showed a 15 x 16 cm, heterogeneously enhanced tumor without regional lymphadenopathy. Right renal vein and inferior vena cava (IVC) thrombosis extending to the right atrium were noted on venocavography. Right radical nephroureterectomy and IVC thrombectomy were performed with cardiopulmonary bypass. Grossly, the tumor measured 14.5 cm in diameter, and the cut surface was grayish white with areas of necrosis and hemorrhage. The IVC thrombus was 15.8 x 3.5 x 3.5 cm in size. Microscopically, the tumor was composed of sheets of loosely cohesive small round cells with fine powdery chromatin in a perivascular arrangement, or separated by fibrous bands. Perirenal soft tissue involvement by tumor cells was also noted. Immunohistochemically, the tumor cells stained positively for neuron-specific enolase (NSE), S-100, vimentin, CD99 and FLI-1, but were negative for cytokeratin, chromogranin and synaptophysin. No molecular analysis was performed on the specimen. The postoperative course was uneventful. Five months later, CT showed multiple hepatic and pulmonary nodules consistent with metastasis. Local tumor recurrence with an IVC thrombus was also noted. The patient did not receive any adjuvant therapy and died of disseminated disease 7 months after diagnosis.

Case 3
A 45-year-old male presented with a 2-month history of intermittent painless hematuria. Intravenous urography (IVU) showed left hydrenephrosis with a filling defect in the left lower ureter and bladder. Cystoscopy revealed a reddish tumor with a granulated surface protruding from the left ureteral orifice. Transurethral resection of the tumor and laser ablation were performed. Pathology showed only squamous metaplasia. Three years later, gross hematuria recurred. Cystoscopy revealed a recurrent tumor bulging from the left ureteral orifice. Left ureteral segmental resection, partial cystectomy, and ureteroneocystostomy were performed. Pathology revealed ureteral PNET. Microscopically, the ureteral tumor was composed of monotonous medium-sized oval to polygonal tumor cells in a sheet-like distribution with slightly irregular, hyperchromatic nuclei and ill-defined cytoplasmic borders. Immunohistochemical staining was positive for NSE, S-100, CD99 and FLI-1, and negative for synaptophysin, chromogranin, common leukocyte antigen and cytokeratin. Recurrence was noted again 7 years later. CT showed left-side hydronephrosis with a huge mass at the pelvic cavity with adhesion to the bladder, pelvic side wall and rectus muscle. Adjuvant chemotherapy was given with a VAC and IE regimen for 3 courses. However, disease progression with lung metastasis was noted. Other drugs, including docetaxel, topotecan and imatinib mesylate, and palliative radiotherapy with 2800 cGy in 14 fractions, were also given. He died of disseminated metastasis 2 years after chemotherapy.

Discussion
PNET is a member of the small round cell tumor family. PNET arising from the urinary tract is a rare disease that has been documented principally through case reports.2–7 The differential diagnosis includes the other members of this family, such as extrasosseous Ewing’s sarcoma, rhabdomyosarcoma, Wilms’ tumor, neuroblastoma, etc.5–8 We analyzed 851 cases of urinary tract malignancy in our hospital between 1984 and 2004, and only three (0.035%) cases of PNET were identified. Our review of the literature found over 100 cases of PNET arising from the urinary tract, and most of these cases arose from the kidney. Primary urinary bladder PNET has been reported once and PNET originating from the ureter (Case 3) has
not been previously reported. Renal PNET and IVC tumor thrombus has only been reported four times and our patient (Case 2) is the fifth reported case.\textsuperscript{10–13}

Histologically, PNET is characterized by small round cells that may form Homer-Wright rosettes or pseudorosettes. PNET can be differentiated from other small round cell tumors by immunohistochemical techniques. PNET may be negative for S-100, synaptophysin, chromogranin, cytokeratin, actin, desmin, and neurofilament. Some stains, such as CD99, FLI-1 and WT-1, are useful to confirm the diagnosis. Nearly all PNETs are strongly CD99 positive, which is a product of the \textit{MIC2} gene. Two recently described nuclear proteins, FLI-1 and WT-1, can discriminate PNET from other small round cell tumors. Approximately 70\% of extrarenal PNETs and 67\% of renal PNETs are positive for FLI-1 antibody.\textsuperscript{5,6} Most renal PNETs did not express WT-1, the product of the \textit{WT-1} gene located at 11p13, which is a transcription factor of the tumor suppressor gene.\textsuperscript{5–8} Approximately 90\% of PNETs have a specific t(11;22)(q24;q12) chromosomal translocation that results in a unique chimeric protein, EWS-FLI-1. Using reverse transcription–polymerase chain reaction, the chimeric gene can be demonstrated as a highly specific molecular marker.\textsuperscript{14} All three cases of PNET in this report stained positively for CD99 and FLI-1.

Most reported cases of PNET typically manifest in children and young adults. Kuroda et al reported that the average age at diagnosis was 27.7 years.\textsuperscript{3} Another large series of renal PNET cases of the kidney showed a wide age spectrum, ranging from 1 month to 72 years, with a median age of 18 years.\textsuperscript{5,6} The two cases of renal PNET in this report were both much older (44 years and 75 years) than the mean age in previous reported series.

It is difficult to differentiate renal PNET from Wilms’ tumor, renal cell carcinoma, and sarcomatous lesions by imaging studies alone. However, PNETs are typically noncalcified ill-defined heterogeneous masses of low attenuation, with necrotic or hemorrhagic areas and only slight contrast enhancement in the solid portions on nonenhanced CT.\textsuperscript{15}

Because of the aggressive behavior and poor prognosis of renal PNET, there has been some debate about whether renal PNET is an entity distinct from extrarenal PNET.\textsuperscript{16–18} Treatment includes surgery, radiotherapy, and multidrug chemotherapy. Prior reports have shown that renal PNET behaves more aggressively than extrarenal PNET. Patients usually present with an advanced stage and show a poor response to combined-modality therapy. Most patients with advanced renal PNET die of progressive disease within 1 year of diagnosis. Given the highly aggressive behavior of this tumor, adjuvant multidrug chemotherapy is still necessary postoperatively. In Case 1 of this report, radical surgery for localized disease combined with adjuvant chemotherapy achieved long-term survival.

PNET of the urinary tract is a rare entity that appears to behave more aggressively than at other locations. The distinction from other primary malignancies of the urinary tract is crucial for prognosis. Immunohistochemical staining is helpful for diagnosis. Only early diagnosis, radical surgery and adjuvant chemotherapy can achieve good results.

\textbf{References}