BRIEF REPORT
Hepatoblastoma and Hypoplastic Kidneys: A New Association

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Both hepatoblastoma and hypoplastic kidneys are rare in children. A review of all patients with hepatoblastoma treated at our institution between 1993 and 2011 revealed three cases of hepatoblastoma occurring in children with hypoplastic kidneys and significantly impaired renal function. Two patients were treated with doxorubicin-based therapy without cisplatin. One was treated with carboplatin. The former two are long-term survivors while the third patient died of sepsis following chemotherapy. This association is unlikely due to chance alone and chemotherapy regimens without cisplatin may be effective in treating these children. Pediatr Blood Cancer 2014;61:1476–1478. © 2014 Wiley Periodicals, Inc.

Key words: cisplatin; dialysis; hepatoblastoma; hypoplastic kidneys; renal failure

INTRODUCTION
Hepatoblastoma is the most common malignant liver tumor in children. Ninety five percent of cases occur in children less than 5 years of age, and males are more commonly afflicted [1]. Hepatoblastoma has been associated with Familial Adenomatous Polyposis, Beckwith-Wiedemann syndrome, hemihyperplasia, and Trisomy 18 [2–4]. In addition, hepatoblastoma has been associated with low birth weight [5]. The association of hepatoblastoma with glomerulocystic and polycystic kidney disease has been suggested previously in isolated case reports [6–11]. We present a single institution experience with a case series of hepatoblastoma occurring in association with hypoplastic kidneys and discuss its management.

RESULTS
We reviewed the medical records and reports of imaging studies from 56 patients with hepatoblastoma treated at our institution between 1993 and 2011. Three patients with hypoplastic kidneys were identified (Table I).

Case 1
A male born at 35 weeks with Potter sequence (bilateral hypoplastic kidneys, oligohydramnios, and bilateral pulmonary hypoplasia), on peritoneal dialysis since 5 weeks of age and erythropoietin treatment for anemia, presented at the age of 2½ years with a 6.5 cm × 4.6 cm × 4.5 cm mass and a second 5.9 cm × 5.3 cm × 5.6 cm exophytic mass in the right lobe of the liver (Fig. 1). Serum α-fetoprotein (AFP) was 43,400 ng/ml. Complete resection was achieved by right hepatectomy. Pathology revealed hepatoblastoma, epithelial subtype with a mixed embryonal and fetal pattern. The patient received four cycles of adjuvant chemotherapy with 5-fluorouracil, vincristine and doxorubicin (5VD). Doxorubicin was administered at 30 mg/m² on Days 1 and 2; 5-fluorouracil 600 mg/m² on Day 1; and vincristine 1.5 mg/m² on Days 1, 8, and 15 in 21-day cycles. Chemotherapy was administered during the day with nightly peritoneal dialysis. The patient experienced one episode of febrile neutropenia with Klebsiella pneumonia bacteremia and one episode of reversible lower extremity neuropathy attributed to vincristine, which was withheld for the final cycle. Myeloid growth factor was administered after each cycle. The patient is in remission 27 months following end of therapy and is currently undergoing evaluation for renal transplant. No karyotype was obtained in this patient.

Case 2
A male born at 30 weeks with bilateral hypoplastic kidneys, chronic renal insufficiency, and hypospadias presented at the age of 22 months with a 9.1 cm × 7 cm × 10 cm mass in the posterior segment of the right lobe of the liver with central necrosis and portal vein invasion. Serum AFP was 498,000 ng/ml. Biopsy showed epithelial-type hepatoblastoma with embryonal histology. GFR measured by technetium-99m diethylene-triamine-penta-acetic acid scan was 22.9 ml/minute/1.73 m². Neoadjuvant chemotherapy consisted of four cycles of 5VD. The tumor decreased to a third of the initial size. He underwent a right-hepatectomy with gross total resection followed by two additional cycles of 5VD. He tolerated the chemotherapy well except for one episode of febrile neutropenia requiring admission to the hospital. He did not require myeloid growth factor support. His renal function remained at baseline until 4 months following therapy when he developed dehydration due to feeding pump failure and was ultimately initiated on dialysis. He underwent a renal transplant 3 years later. He is now off therapy for 47 months with no evidence of disease. High resolution chromosome analysis from the peripheral blood revealed a 9p24.2 deletion.

Case 3
A term male was diagnosed at birth with VATER (Vertebral defects, Anal atresia, T-E fistula with esophageal atresia, Radial, and Renal dysplasia) association when he presented with an

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imperforate anus and hypoplastic solitary left kidney requiring hemodialysis. He presented at 6 years of age with multiple large nodular masses throughout the right lobe of the liver, a mass in the medial segment of the left lobe and a 3 cm × 1.5 cm lymph node adjacent to the liver. Serum AFP was 113,520 ng/ml. Open liver biopsy revealed multifocal predominantly-poorly-differentiated hepatoblastoma with extensive necrosis and scattered sections exhibiting embryonal morphology. Neoadjuvant chemotherapy was started with single agent carboplatin 350 mg/m² given as a single dose immediately after hemodialysis. Nine days after the initiation of chemotherapy, the patient was admitted with septic shock due to Klebsiella and Enterobacter species infection. His clinical condition continued to deteriorate despite broad-spectrum intravenous antibiotics and inotrope support, and he died of cardiopulmonary failure 6 days later. No karyotype was obtained in this patient.

DISCUSSION

We report on three children with hepatoblastoma and hypoplastic kidneys diagnosed at our institution. Two are alive and in remission. The incidence of hypoplastic kidneys in our population of hepatoblastoma patients is 3 in 56 patients, or 535 per 10,000 patients. In contrast, the incidence of all kidney dysplasia (including hypoplasia) is less than 1 per 10,000 births [12]. A Children’s Oncology Group study found that children with hepatoblastoma were five times more likely to have kidney/bladder abnormalities when compared to age-matched controls [13]. In addition, isolated case reports suggest an association of congenital kidney defects with hepatoblastoma [6–10]. In three of these reports, hepatoblastoma occurred in male children with glomerulocystic disease and liver fibrosis. Although treatment details were missing, all three patients died. In a more recent report, hepatoblastoma developed in a male patient with autosomal recessive polycystic kidney disease [11]. Monotherapy with reduced-dose doxorubicin was given following complete resection. This patient was in remission for 10 months at the time this case was reported. It is interesting to note that all patients but one reported with hepatoblastoma and kidney disease in the medical literature including ours were male.

Cisplatin is the most active chemotherapy agent in hepatoblastoma [14]. Its major side effects include nephrotoxicity and ototoxicity. Significantly reduced renal function in general

### TABLE I. Clinical Characteristics

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<thead>
<tr>
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<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
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<tbody>
<tr>
<td>Age at diagnosis</td>
<td>29 months</td>
<td>22 months</td>
<td>6 years</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>Presentation</td>
<td>Incidental finding during renal transplant evaluation</td>
<td>Palpable abdominal mass</td>
<td>Palpable abdominal mass</td>
</tr>
<tr>
<td>Congenital renal condition</td>
<td>Bilateral hypoplastic kidneys</td>
<td>Bilateral hypoplastic kidneys</td>
<td>Solitary hypoplastic kidney</td>
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<td>Other anomalies</td>
<td>Pulmonary hypoplasia</td>
<td>Hypospadias</td>
<td>VATER</td>
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<td>Children’s Oncology Group stage</td>
<td>Stage I</td>
<td>Stage III</td>
<td>Stage III</td>
</tr>
<tr>
<td>Histology</td>
<td>Mixed epithelial- fetal and embryonal</td>
<td>Embryonal</td>
<td>Embryonal</td>
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<tr>
<td>Treatment</td>
<td>Surgery, 4 cycles of 5VD</td>
<td>4 cycles of 5VD, surgery, 2 cycles of 5VD</td>
<td>1 cycle of carboplatin</td>
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<td>Complications</td>
<td>Neutropenic sepsis, vincristine neuropathy</td>
<td>Neutropenic fever</td>
<td>Septic shock</td>
</tr>
<tr>
<td>Outcome</td>
<td>Alive, 27 months off-therapy</td>
<td>Alive, 47 months off-therapy, now with renal allograft</td>
<td>Died after 1 cycle due to sepsis</td>
</tr>
</tbody>
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VATER, Vertebral defects, Anal atresia, T-E fistula with esophageal atresia, Radial and Renal dysplasia; 5VD: fluorouracil, vincristine, doxorubicin.

Fig. 1. A: Ultrasonographic appearance of kidney at birth of Case 1. It is severely hypoplastic. B: Appearance of liver tumor via computed tomography at the time of diagnosis (white arrow), as well as hypoplastic kidney (black arrow).

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precludes cisplatin therapy. Hoping to preserve remaining renal function, we used a doxorubicin-based backbone with case 2. Nephrotoxicity was not a direct concern for cases 1 and 3, as they already had end-stage renal disease (ESRD) and were dependent on renal replacement therapy. Cisplatin has been administered to a patient with hepatoblastoma and anuric renal failure [15]. Its clearance via dialysis may be inefficient with a half-life of up to 5 days [16]. Anticipating that extended exposure to cisplatin could result in significant hematopoietic toxicity and ototoxicity, we did not administer cisplatin to patients 1 and 3.

It is interesting to note the 9p24 deletion in case 2, which has no previously known association with hepatoblastoma or renal dysplasia/hypoplasia. While defects on chromosomes 1, 2, 5, 6, and 10 have recently been described in patients with renal agenesis, the significance of the 9p deletion remains unclear [17]. Recognizing that hypoplastic kidneys may be the end result of several different genetic mutations, we are currently collecting peripheral blood from patients with hepatoblastoma and renal defects diagnosed at our institution and other institutions across the country to further define the genetic basis of this association.

While hepatoblastoma is a rare tumor, its association with hypoplastic kidneys and ESRD may be higher than previously appreciated. Given the challenges of administering chemotherapy in the setting of impaired renal function, safe therapy options are needed for children who have hepatoblastoma and renal failure. Based on our experience, a doxorubicin-based regimen without cisplatin may be a reasonable option. In addition, the occurrence of hepatoblastoma in patients with congenital underlying renal dysfunction suggests a developmental and/or genetic basis and should be investigated.

REFERENCES