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Case Report

Acquired Multiple Cysts of the Kidney in Neuroblastoma Survivors

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Cystic kidney disease includes a wide range of hereditary, developmental, and acquired conditions of the kidneys. Some of the inherited causes of cystic kidney disease include autosomal dominant polycystic kidney diseases (caused by mutations in *PKD1* or *PKD2*), autosomal recessive polycystic kidney disease, tuberous sclerosis complex, von Hippel-Lindau disease, oral-facial-digital syndrome type I, and Hadju-Cheney syndrome. Acquired cystic kidney disease has been reported in patients receiving long-term hemodialysis or peritoneal dialysis and in children after liver transplantation. Acute kidney injury can occur in patients with neuroblastoma, usually as a result of thrombotic microangiopathy associated with bone marrow transplantation. End-stage renal disease is described in long-term survivors. However, in this case report, we provide what is to our knowledge the first description of multiple kidney cysts in long-term survivors of stage IV neuroblastoma. None of the 7 patients we describe with neuroblastoma and multiple kidney cysts had a family history of autosomal dominant polycystic kidney disease. Also, all lacked stigmata of tuberous sclerosis complex, von Hippel-Lindau disease, or Hadju-Cheney syndrome. Two patients progressed to end-stage renal disease; in addition, one of them developed an oncocytoid renal cell carcinoma.
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INDEX WORDS: Chronic kidney disease (CKD); cystic kidney disease; multiple renal cysts; neuroblastoma; ultrasound; computed tomography; magnetic resonance imaging; acquired cystic kidney disease; case report.

Although long-term survivors of neuroblastoma stages III and IV may develop chronic kidney disease (CKD), to our knowledge, there are no reports of kidney cysts in such patients. In this report, we describe 7 long-term survivors of neuroblastoma in whom we detected features of multiple kidney cysts. These findings were similar to those seen in autosomal dominant polycystic kidney disease (ADPKD). None of these patients had a family history of ADPKD or findings of liver cyst on imaging. Also, none of these patients had features of tuberous sclerosis complex, von Hippel-Lindau disease, or Hadju-Cheney syndrome. Similar findings of kidney cysts have been reported in patients receiving long-term dialysis and in children after liver transplantation. The purpose of this report is to describe the clinical presentations and imaging findings of these 7 patients and discuss the clinical management of long-term survivors of neuroblastoma who have multiple kidney cysts.

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CASE REPORTS

We retrospectively reviewed the medical charts (dated 2000 to 2012) of 7 patients who had neuroblastoma and developed multiple kidney cysts following neuroblastoma treatment. Demographic information and family history were collected, revealing that most patients were male and white and none had a family history of ADPKD.

Clinical and laboratory data were abstracted from the records of each nephrology clinic visit. Clinical data included the origin, staging, and type of neuroblastoma and complications of neuroblastoma treatment. All patients had stage IV neuroblastoma on initial diagnosis. Neuroblastoma was detected between the ages of 2 and 3 years (median age at presentation, 2 years 7 months). Neuroblastoma involved the adrenal glands (patients 2 and 4), abdomen (patients 1, 5, and 8), and flank region (patients 6 and 7). Neuroblastoma metastasized to the face, skull, sternum, right femur, right flank, and thoracic spine in patient 2 and to the skull in patient 7. All patients received chemotherapy and total-body irradiation prior to bone marrow transplantation. Table 1 details these clinical data.

Laboratory data included serum creatinine concentration (in mg/dL), urine protein-creatinine ratio (in mg/mg), and urine microalbumin-creatinine ratio (in μg/mg). Estimated glomerular filtration rate (eGFR) was calculated using the revised Schwartz formula[1] for patients younger than 18 years and the MDRD (Modification of Diet in Renal Disease) Study equation for patients 18 years or older. CKD was defined as the presence of 3 or more months of decreased eGFR rate or persistent proteinuria. Nephrotic-range proteinuria was defined as spot urine protein-creatinine ratio >2 mg/mg; non–nephrotic-range proteinuria, as a ratio >0.2 and <2 mg/mg. Results from kidney ultrasounds, computed tomographic (CT) scans, and magnetic resonance (MR) images were noted.

Several endocrine-related side effects, perhaps related to total-body irradiation, included diabetes (57%), hypothyroidism (71%), short stature (71%), and gonadal failure (29%). Bilateral cataracts developed in 57% of patients. Four of 5 (80%) patients who received doxorubicin developed cardiomyopathy, and 3 of 5

Table 1. Location, Staging and Treatment of Stage IV Neuroblastoma

Case	Tumor Location	Sex	Chemotherapy	Radiation Therapy	BMT
1	Abdomen	M	Doxorubicin, cisplatin, vincristine	Total-body irradiation	Y
2	Adrenal gland, R	M	Etoposide, thiotepa, cyclophosphamide, MIBG therapy, carboplatin, vincristine, cisplatin	Local radiation to area of tumor, sites of bone metastasis (face and skull, sternum, right distal femur, right flank, and thoracic spine) and total-body irradiation	Y
3	Adrenal gland, L	M	Doxorubicin	Total-body irradiation	Y
4	Abdomen	M	Doxorubicin	Total-body irradiation	Y[a]
5	Flank, R	F	Doxorubicin, cisplatin, etoposide, carboplatin, melphalan, cyclophosphamide	Local radiation to right flank and total-body irradiation	Y
6	Flank, L	M	Doxorubicin, cisplatin, etoposide, carboplatin, thiotepa, cyclophosphamide, vincristine	Local radiation to left flank and sight of metastasis in skull and total-body irradiation	Y
7	Abdomen, R	M	Etoposide, carboplatin, melphalan, cyclophosphamide, anthracycline	Local boost to primary retroperitoneal bed and total-body irradiation	Y[a]

Abbreviations: BMT, bone marrow transplant; L, left; MIBG, meta-iodo-benzyl-guanidine; R, right.
[a]Two stem cell transplants.

(60%) patients who received cisplatin or carboplatin developed bilateral sensorineural hearing loss. All patients developed multiple cysts in both kidneys and developed CKD. Median time from the diagnosis of neuroblastoma to onset of CKD was 10 years. Three patients developed nephrotic-range proteinuria (patients 1, 3, and 6) and 3 developed non–nephrotic-range proteinuria (patients 2, 4, and 5). Two patients progressed to end-stage renal disease: patient 1 was treated with long-term peritoneal dialysis and patient 3 initially received long-term peritoneal dialysis and then transitioned to continuous venovenous hemodialysis during the last 2 months of his life. In addition, patient 3 developed an oncocytoid renal cell carcinoma of the right kidney with metastasis, for which he underwent right nephrectomy and received chemotherapy.

In 4 of 7 patients (patients 1, 4, 6, and 7), ultrasounds, CT scans, and/or MR images were chosen on the basis of available studies demonstrating the appearance of the kidneys before and after the development of bilateral kidney cysts. In 3 of 7 patients (patients 2, 3, and 5), images of the kidneys prior to developing kidney cysts were not available. Mean age at detection of multiple kidney cysts was approximately 14 (range, 5-18) years. Atrophy of the kidney ipsilateral to the treated neuroblastoma, likely related to past radiation therapy, was seen on follow-up imaging in 5 of 7 patients (patients 2, 3, 5, 6, and 7).

Patient 1 was approximately 2 years of age when stage IV neuroblastoma was diagnosed; imaging was available from 1985 to 2007 (corresponding to ages 2 to 24). From 2 to 9 years of age, the kidneys (by ultrasounds and CT scans) were normal. Bilateral kidney cysts were evident within each kidney in follow-up imaging studies performed when the patient was 18 to 24 years of age.

Patient 2 was approximately 3 years of age when stage IV neuroblastoma was diagnosed. Imaging was available from 2005 to 2007; when the patient was 18 and 20 years old, respectively, CT scan and ultrasound revealed bilateral kidney cysts.

For patient 3, who had stage IV neuroblastoma diagnosed at 2 1/2 years of age, imaging was available from 2003 to 2005, when he was aged 15 to 17 years. Ultrasounds, CT scans, and MR images demonstrated bilateral kidney cysts.

Patient 4, who was approximately 2 years old when stage IV neuroblastoma was diagnosed, had imaging data from 2000 to 2011 (corresponding to ages 5 to 16 years). From 5 to 8 years of age, the kidneys (on CT scans) were normal. Bilateral kidney cysts were evident within each kidney in follow-up imaging studies performed at ages 11 to 16 years.

Patient 5 was approximately 3 years of age when stage IV neuroblastoma was diagnosed; CT scans and ultrasounds (available from 2005 to 2007, when she was aged 18 and 20 years, respectively) demonstrated bilateral kidney cysts. Figure 1 demonstrates atrophy of the left kidney in this patient.

Patient 6 was approximately 3 years of age when stage IV neuroblastoma was diagnosed. From ages 3 to 5 years, the kidneys (on ultrasounds) were normal, but by 5 years, atrophy could be noted in the left kidney. Bilateral kidney cysts were evident within each kidney at follow-up imaging studies performed at 18 to 20 years of age.

Patient 7, approximately 2 1/2 years of age when stage IV neuroblastoma was diagnosed, had imaging data available from 2006 to 2011 (up to age 8 years). In 2006, on pre- and post-treatment images, the kidneys (on CT scans) were normal. Bilateral kidney cysts were evident on follow-up imaging studies performed at ages 7 to 8 years.

DISCUSSION

Cystic kidney diseases in children can be classified as either inherited or acquired. ADPKD, the most common hereditary cystic kidney disease, is characterized by the development of multiple macroscopic kidney cysts. Less common genetic causes of dominantly inherited cystic kidney disease include tuberous sclerosis complex,[2] von Hippel-Lindau disease,[3] oral-facial-digital syndrome type I,[4] and Hadju-Cheney syndrome.[5]

There have been reports of patients treated with long-term hemodialysis or peritoneal dialysis developing cystic kidney disease.[6,7] The development of multiple cysts in these often contracted kidneys could be due to the accumulation of a uremic metabolite that acts as a proliferative factor and aids cystic transformation within the kidneys.[6,7] In children,