Intracranial calcification in a uremic infant with Wilms' tumor in a solitary kidney

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Received: 30 January 2012 / Accepted: 9 May 2012 / Published online: 8 June 2012
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Abstract Wilms' tumor (WT), also called nephroblastoma, is an embryonic neoplasm of the developing kidney. A previously healthy Japanese female infant had WT in a single kidney without associated congenital malformations. Preoperative chemotherapy was started for the preservation of renal tissue and function. Tumor lysis syndrome, disseminated intravascular coagulopathy, and acute renal failure were accompanying. The infant needed surgical intervention and permanent replacement therapy. At the start of emergency hemodialysis, the infant had posterior reversible leukoencephalopathy syndrome because of severe hypertension. During ongoing peritoneal dialysis, the infant suffered from anemia, dietary and fluid restriction, and restriction of time and mobility. Despite alfacalcidol and calcium supplementation, the infant had secondary hyperparathyroidism and remarkably short stature. After waiting for the completion of chemotherapy, renal transplantation from the mother was completed. Successful kidney transplantation promptly corrected preexisting metabolic

abnormalities causing secondary hyperparathyroidism. Subsequently, the infant often complained of headache. Computed tomographic scanning revealed calcification in the cerebellum. Refractory secondary hyperparathyroidism was inferred as the cause. A well-functioning graft provided the infant with a greater sense of well-being and enabled her to enjoy a lifestyle free of dialysis, although the infant must continue taking transplant medications and has retained unresolved issues of short stature and ectopic intracranial calcification.

Keywords Calcification · Secondary hyperparathyroidism · Renal transplantation · Short stature · Wilms' tumor

Introduction

Wilms' tumor (WT), the most common renal cancer in children, is associated with certain congenital anomalies: genitourinary malformation, hemihypertrophy, sporadic aniridia, cryptorchidism, Beckwith–Wiedemann syndrome, Denys–Drash syndrome, and WAGR syndrome (WT, aniridia, genitourinary malformation, and mental retardation) [1]. A dramatic rise in the WT survival rate to 90 % occurred when multimodal therapeutic approaches were adopted, although the treatment of WT in a solitary kidney has persisted as a clinical challenge [2]. The National Wilms Tumor Study Group (NWTSG) has recommended preoperative chemotherapy under certain circumstances, including WT occurrence in a solitary kidney, bilateral WT, tumor in a horseshoe kidney, tumor thrombus in the inferior vena cava above the level of the hepatic veins, and respiratory distress resulting from the presence of extensive metastatic tumor [2]. Intracranial calcification occurs in

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various pathological and physiological conditions, including a change secondary to infection, metabolic disease, familial disorders, and medical treatment [3–6].

This report describes an infant with WT in her single kidney, who needed permanent replacement therapy. Cerebellar calcification on computed tomographic (CT) scan was observed after kidney transplantation. Possible causes of distant extraskeletal calcifications in the central nervous system (CNS) and the efficacy and subjects waiting solution of kidney transplantation have been described.

Case report

A 2-year-old Japanese girl was referred to us because of abdominal pain, abdominal distention, and gross hematuria. Her previous medical history was unremarkable. The growth, development, and appearance of her genitalia were normal. Abdominal CT scan showed a huge WT affecting the solitary functioning left kidney. Both intravenous pyelography and renal scintigraphy failed to demonstrate the right kidney. Open biopsy of the tumor confirmed the diagnosis of WT, with favorable histology. She showed no genetic syndrome associated with WT. Genetic analysis of the WT1 gene was not performed. Chest CT scan revealed lung metastasis. A preoperative chemotherapy regimen was started immediately, with DD-4A consisting of actinomycin D,

vincristine, and doxorubicin, according to the NWTSG-5 recommendation for stage IV. Tumor lysis syndrome with acute renal failure and disseminated intravascular coagulopathy developed 6 days after the first dose of chemotherapy, necessitating emergency hemodialysis and radical nephrectomy. The removed tumor was 14×8 cm, weighing 590 g. A few days after starting hemodialysis, she suddenly had generalized tonic-clonic convulsion, followed by frequent vomiting, with hypertension of 180/120 mmHg. Her blood sugar and serum electrolytes were normal. Head CT scan showed no intracranial hemorrhage or brain edema. Seizures were controlled by intravenous infusion of 3 mg of diazepam, with continuous infusion of midazolam at 0.5 mg/kg/h. The next day, she had another seizure and received rapid bolus infusion of phenytoin, followed by a maintenance dose of 5 mg/kg/day for 2 days. Intravenous administration of hydralazine hydrochloride at a dose of 0.1 mg/kg/dose and nicardipine hydrochloride at a dose of 2.0 mcg/kg/min were started in order to control hypertension. Magnetic resonance imaging (MRI) of the brain was highly compatible with posterior reversible leukoencephalopathy syndrome. Subsequently, hemodialysis was replaced by continuous cyclic peritoneal dialysis (CCPD) using regular calcium (2.5 mEq/l). Although no peritonitis occurred, she had massive fluid overload with a positive fluid balance. Chest X-ray results showed an enlarged heart with a cardiothoracic ratio (CTR) of 63 %. Echocardiography was normal. For more adequate fluid management, dialysate was changed to icodextrin peritoneal dialysis solution. The clinical course, including the levels of serum calcium, phosphate, and intact parathyroid hormone (PTH), is presented in Fig. 1. Continuing CCPD while receiving chemotherapy, she suffered continually from anemia, dietary and fluid restriction, and restriction of time and mobility. About 6 months after

Fig. 1 Clinical summary of serum calcium and phosphate and intact parathyroid hormone levels, and date of the treatment. This graph shows the clinical course of our patient from presentation until the appearance of cerebellar calcification after kidney transplantation: CCPD continuous cyclic peritoneal dialysis; Chemotherapy DD-4A consisting of actinomycin D, vincristine, doxorubicin, HD hemodialysis, iPTH intact parathyroid hormone, PRES posterior reversible encephalopathy syndrome

Fig. 2 The head computed tomographic scan shows two clusters of calcification in the bilateral cerebellar hemisphere (encircled)

starting CCPD, she had an elevated calcium–phosphorus product, the highest being $88.35 \text{ mg}^2/\text{dl}^2$, with an intact PTH of 900–1200 pg/ml. These values gradually improved after the completion of chemotherapy. Before kidney transplantation, her calcium–phosphorus product was $50\text{--}65 \text{ mg}^2/\text{dl}^2$, with a PTH of 100–500 pg/ml. Hand X-rays showed no subperiosteal resorption. Oral alfacalcidol $0.03 \text{ }\mu\text{g/kg/day}$ and calcium carbonate 0.5 g/day were given, but they were refused. The mother, actually sitting by her bedside, almost gave up care in frustration because of the numerous responsibilities she fulfilled for her daughter, who had been on CCPD for 1 year and 10 months. At the age of 4 years and 3 months, kidney transplantation from the mother was chosen. All serum calcium, phosphate, and intact PTH levels were promptly normalized, although her growth was significantly retarded. Her height was 86.2 cm [-3.2 standard deviation (SD)]. Her weight was 11.4 kg (-1.9 SD). Six months later, she often complained of a headache, but had normal blood pressure. A head CT scan showed a few small foci of calcifications in the cerebellar hemisphere (Fig. 2). Serum cytomegalovirus antigen (C7-HRP) and toxoplasmosis antibodies were all negative and ophthalmologic examination was normal. MRI showed no brain tumor or metastasis. Headache subsided with nonsteroidal anti-inflammatory medications. No other extraskeletal calcification was found. During the 7 years of follow-up after transplantation, her transplanted kidney function remained normal and she had no recurrent WT. Repeated head CT scans showed no new calcification. She showed gradual catch-up growth without neurological sequelae. She enjoyed playing soccer with her elder sister.

Discussion

Intracranial calcifications are infrequent in children, but they often constitute a clue to the disease. Seizure was the most common presentation, occurring in 55 % of cases, whereas headache accounted for a considerably low percentage of 2.9 % of cases [3]. Other symptoms included failure to thrive, cerebral palsy, weakness, syncope or fainting, microcephaly, cranial asymmetry, mental or motor retardation, and others [3, 4]. A case of tuberculoma with cerebellar calcification showed ataxia [4]. In contrast, none of five patients with cerebellar calcifications showed symptoms or signs of cerebellar disease [7]. No cerebellar symptoms were present in our case.

The common sites of physiological calcifications were the pineal and choroid plexus, but the prevalence was <2 % below the age of 9 years [3, 5]. By far the most common cause of pathological calcifications are brain tumors [3, 5]. In our patient, both CT scan and MRI showed no brain tumor or metastasis, although no brain biopsy was performed.

Our patient had no intracranial hemorrhage causing a chronic subdural hematoma and old intraventricular bleeding, which probably accounted for intracranial calcifications [3, 5, 6]. Calcification in old cerebral infarction is rare [4]. Typical calcification patterns diagnostic of Sturge–Weber syndrome, arteriovenous malformations, and intracerebral cyst were not present in our patient [4, 6].

Basal ganglia calcification occurred in idiopathic hyperparathyroidism, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome, Cockayne syndrome, Leigh disease, and Fahr syndrome [3, 4, 6]. Before nephrectomy, calcium homeostasis was normal. Basal ganglia calcification was not observed in our patient.

Other nontumoral causes such as toxoplasmosis, cytomegalovirus, rubella, post-meningitis, aneurysm of the vein of Galen, birth asphyxia and ischemic episodes, demyelination, and folate deficiency-induced calcification were not observed in our patient [3, 4, 6, 8]. Faint homologous calcification in the cerebellum has been reported in a case of tuberculoma, but our patient had no primary tuberculosis [4].

Radiation and chemotherapy have been implicated in the appearance of marked detrimental effects on the CNS [6]. Radiation-related and chemotherapy-related calcifications more frequently occurred in younger children than in adult patients [6]. For the treatment of lung metastasis, our patient was given 12 Gy of whole-lung irradiation with chemotherapy, which might be responsible for intracranial calcification.

Another possible cause of extraosseous calcification was secondary hyperparathyroidism associated with chronic kidney disease (CKD). In patients with CKD, the CNS is one of the most common sites of extraskeletal calcification [9]. Secondary hyperparathyroidism is a common complication of CKD, causing morbidity in children, including renal osteodystrophy (CKD-MBD), and impaired growth, leading to short stature as a young adult [10]. Recently, secondary hyperparathyroidism has been associated with an increased risk of vascular calcification and cardiovascular morbidity in young adults with childhood-onset CKD, even after successful kidney transplantation [11]. For better control of secondary hyperparathyroidism, it is imperative to correct any fluid and electrolyte imbalance and concomitant acidosis, and to use hydroxylated vitamin D and calcium supplementation judiciously [10, 12]. When receiving chemotherapy, our patient was not very tolerant: dependence on the treatment and maintenance of peritoneal dialysis induced a loss of self-esteem and emotional maladjustment [13]. The anorexic patient just picked at her meals and would never take medication at all. The replacement of dialysate with icodextrin and avoidance of high phosphate-containing foods did not improve

metabolic abnormalities, especially in receiving chemotherapy. An alternate treatment with low calcium peritoneal dialysate, more strict dietary phosphorus restriction, and substitution of calcium-based phosphorus binders with sevelamer should be attempted [12].

Little is known about treatments and outcomes for children who have end-stage renal disease (ESRD) after treatment for WT. ESRD is one of the most serious late sequelae due to the morbidity of treatment and high mortality. The most favored treatment modality in children with ESRD is kidney transplantation. Early reports recommended delaying transplant for 1–2 years following WT treatment because of deaths due to sepsis and tumor recurrences observed in patients undergoing transplant sooner [14, 15]. European best-practice guidelines for renal transplantation recommended a 2-year waiting period [16]. Recently, the recommended waiting time of transplant in relation to WT treatment has been reevaluated. Grigoriev et al. [17] proposes that WT patients who subsequently develop ESRD can immediately be considered as candidates for kidney transplant and not subject to a 2-year wait time, although there is no firm statistical evidence to support early transplant because of the small numbers of patients.

The mobility and freedom from dietary restriction afforded by functioning kidney transplantation enabled our patient to live a nearly normal life. Studies of the quality of life after kidney transplantation have revealed that one-third of patients with functioning grafts of more than 10 years were dissatisfied with their body appearance and were concerned about their short stature and poor bone health [11]. Recombinant human growth hormone (rhGH) has been used to improve growth retardation associated with CKD and ESRD. Because the therapeutic use of rhGH has caused concern that it might increase the risk of tumor recurrence in those previously treated for a malignancy, rhGH has not been administered in our case [18]. After successful kidney transplantation, she not only had some issues including short stature and distant calcification in the CNS, but she also had to continue taking transplant medications. Therefore, long term and careful follow-up are necessary in order to support her and to safeguard her future.

Conflict of interest The authors declare that no conflict of interest exists.

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