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Development of Anaplastic Wilms Tumor and Subsequent Relapse in a Child with Diaphanospondylodysostosis

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Abstract

Diaphanospondylodysostosis (DSD) is a rare skeletal dysplasia syndrome resulting from disordered mesenchymal differentiation. Children with DSD generally die *in utero* or during the first month of life from severe thoracic insufficiency syndrome. An association of DSD with nephroblastomatosis has been observed, but the natural history of such nephroblastomatosis remains poorly characterized due to the rarity of the underlying condition. We describe a patient with DSD who developed bilateral hyperplastic nephroblastomatosis that ultimately evolved into therapy-resistant anaplastic Wilms tumor (nephroblastoma).

Keywords

nephroblastomatosis; Wilms tumor; diaphanospondylodysostosis; skeletal dysplasia; predisposition

INTRODUCTION

Diaphanospondylodysostosis (DSD) is a rare, autosomal recessive skeletal dysplasia syndrome of disordered mesenchymal differentiation that is characterized by abnormal vertebral ossification and thoracic insufficiency secondary to a small bell-shaped chest cavity and rib abnormalities.[1–6] Other clinical features of DSD include short neck, ocular hypertelorism, depressed nasal bridge, low-set ears, and an association with

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nephroblastomatosis. Mutations in *BMPER*, the bone morphogenetic protein-binding endothelial cell precursor-derived regulator, have been recently identified in some patients with DSD.[5] To date, fewer than 20 patients with this syndrome have been described, nearly all of whom have expired *in utero* or shortly after birth due to profound respiratory failure. We describe in this report a 4 year and 10 month old male with DSD (the oldest known patient with this syndrome) and congenital multicystic kidneys who developed bilateral intralobar and perilobar nephroblastomatosis by 19 months of age, progressed to Wilms tumor, and eventually died of relapsed anaplastic Wilms tumor despite aggressive multi-modal therapy.

CASE REPORT

This patient was born to non-consanguineous parents of Northern European ancestry following an uncomplicated pregnancy of his G2P2 mother, who received excellent prenatal care. The patient developed respiratory distress immediately after birth, requiring intubation and mechanical ventilation in the neonatal intensive care unit. Dysmorphic features were noted in the neonatal period (macrocephaly, short neck, incomplete vertebral ossification, bell-shaped thorax, multiple missing ribs, sacral agenesis, and enlarged multicystic kidneys) and have been previously described (Case 6 in reference[4]). Later clinical features included bilateral inguinal hernias, generalized hypotonia, poor oral feeding, gross motor delay, and diminished expressive speech, although his receptive speech seemed relatively age-appropriate. A gastrostomy tube was placed at 13 months of age to maximize enteral nutrition and minimize aspiration risk. The patient underwent tracheostomy at 14 months old with home mechanical ventilation and, later, staged Vertical Expandable Prosthetic Titanium Rib (VEPTR™) surgeries due to progressive thoracic insufficiency (Figure 1A). The parents' first child, also male, has remained healthy without similar anomalies.

Given the observed occurrence of nephroblastomatosis in other patients with DSD[4] and this patient's congenital multicystic kidneys, he was monitored with serial renal ultrasounds and diagnosed with biopsy-proven multi-focal perilobar and intralobar hyperplastic nephroblastomatosis in both kidneys at 19 months of age (Figure 1B and 1C). No genetic studies were performed on the biopsy material at the referring hospital. The patient's vital signs at initial presentation to our institution were within normal ranges for age with a blood pressure 88/56, pulse 94, and respiratory rate 28 with oxygen saturation 99% on a home pressure support (PS) ventilator. Due to his fragile pulmonary status, the numerous nephrogenic rests, and the unknown natural course of DSD-associated nephroblastomatosis, the patient was treated with 18 weeks of vincristine (0.05 mg/kg/dose) and dactinomycin (0.023 mg/kg/dose for two doses, then 0.045 mg/kg/dose for subsequent doses) per the Regimen EE-4A for low-risk Wilms tumor[7] and tolerated therapy well. Serial magnetic resonance imaging (MRI) of his abdomen and pelvis, chosen due to inadequacy of ultrasound to distinguish definitively his underlying renal cysts from the nephrogenic rests, revealed complete or partial response of his nephroblastomatosis. Two (both left-sided) of the five largest lesions did not abate completely during therapy, but were considered stable disease or possibly scar.

Disease progression was noted in the left kidney at six months off therapy on follow-up MRI. A second course of EE-4A therapy[7] with vincristine 0.05 mg/kg/dose and dactinomycin 0.045 mg/kg/dose was administered, but disease progression was again noted at the end of this therapy. Biopsy of the left renal lesions was planned, but not performed due to occurrence of a massive spontaneous left renal hemorrhage, raising suspicion for evolution of the nephroblastomatosis to Wilms tumor. The patient was too medically fragile to undergo immediate nephrectomy, so was treated with whole abdomen radiation therapy (10 Gy) with a boost to the left kidney (10.5 Gy). Additional systemic therapy, including

doxorubicin-based regimens, was withheld due to his co-morbidities and clinical status at the time. His disease remained stable in both kidneys for approximately nine months, when progression of the left lesions was again observed on MRI. The patient underwent radical left nephrectomy and was noted intra-operatively to have visible bilateral nephroblastomatosis, left renal capsular rupture, and bloody ascites. Histopathologic analysis of the nephrectomy specimen revealed viable anaplastic Wilms tumor (Figure 1D) and numerous perilobar nephrogenic rests (not shown).

The patient subsequently received five cycles of vincristine, enteral irinotecan, and temozolomide (VOIT)[8] as adjuvant therapy for presumed microscopic residual disease. This regimen was ultimately poorly tolerated and resulted in ulcerative colitis discovered by endoscopic biopsy. He was thus observed for approximately three months without further anti-cancer therapy, but developed increasing abdominal distention and discomfort. MRI revealed a large new retroperitoneal tumor originating in the left nephrectomy bed and crossing into the right abdomen (Figure 2A). Exploratory laparotomy was performed to debulk the tumor (Figure 2B), but also revealed small metastases in the mesentery and small bowel. Histopathologic analysis of the primary mass revealed poorly-differentiated Wilms tumor with rhabdomyomatous features (Figure 2C). The tumor demonstrated scattered myogenin, mixed membranous and cytoplasmic epidermal growth factor receptor, and scant focal nuclear WT-1 by immunohistochemical staining (not shown).

The patient subsequently received two cycles of vincristine 1.5 mg/m^2/dose and doxorubicin 45 mg/m^2/dose dosed per Regimen DD-4A[7,9] with dexrazoxane 450 mg/m^2 prior to each doxorubicin dose for cardioprotection, followed by additional whole abdomen (10.8 Gy) and tumor boost (14.4 Gy) radiation. Despite salvage therapy, his abdominal distention continued to increase markedly over the subsequent five months. He remained without radiographic evidence of pulmonary metastasis (not shown). Due to the patient's co-morbidities and poor response to multi-modality therapy, his family elected to pursue palliative care with home hospice. He succumbed to his relapsed Wilms tumor at the age of 4 years and 10 months, the oldest known patient with DSD and the only patient with DSD-associated Wilms tumor to our knowledge.

DISCUSSION

Wilms tumor is the most common embryonal malignancy of the kidney and is not infrequently associated with congenital anomalies. Approximately 10–15% of Wilms tumors are attributed to genetic predisposition syndromes, such as the WAGR and Denys-Drasch syndromes associated with *WT1* mutations.[10] Increased risk of Wilms tumor also occurs in the Beckwith-Wiedemann syndrome, uncommon familial syndromes associated with *FWT1* and *FWT2* mutations, and various other constitutional and tumor-associated genetic alterations that have been described in detail elsewhere.[10–12] In addition, patients with vertebral anomalies, including spina bifida, may have an increased risk of Wilms tumor.[13,14]

Nephrogenic rests (persistent metanephric remnants occurring in fully developed kidneys) are classified as nephroblastomatosis when multifocal or diffuse. These embryonal remnants may be intralobar or perilobar in location and are considered pluripotential; they may senesce entirely or undergo neoplastic evolution.[15] Perilobar rests, as seen in this patient, are strongly associated with evolution to bilateral Wilms tumors.[15] To our knowledge, an association between nephroblastomatosis and polycystic kidney disease has not been reported.

Due to the observed association of DSD with nephroblastomatosis, this patient was appropriately monitored from birth with serial renal ultrasounds. He underwent biopsy of

multiple lesions in both kidneys when new abnormalities were first detected via imaging. Histopathologic examination at that time revealed perilobar hyperplastic nephroblastomatosis and no evidence of Wilms tumor. He was initially evaluated at another cancer center, but no therapy was recommended due to his DSD and significant medical co-morbidities. Due to concern for potential worsening of the patient's respiratory status should the nephrogenic rests grow further or undergo neoplastic transformation, we elected cautiously to treat his hyperplastic nephroblastomatosis with vincristine and dactinomycin, as has been recommended by Beckwith and other experts.[16,17] Unfortunately, his nephroblastomatosis indeed evolved into Wilms tumor, which spontaneously ruptured and likely seeded the retroperitoneal space. Despite whole abdomen radiation therapy, radical nephrectomy, and adjuvant chemotherapy, he developed recurrent Wilms tumor with diffuse anaplasia that ultimately proved recalcitrant to multi-modal therapy. No autopsy was performed, so it is unknown whether or not his right-sided nephroblastomatosis also evolved into Wilms tumor or if he developed occult distant metastasis.

Point mutations in *BMPER* resulting in premature stop codons have been recently reported in tissues from four patients with DSD.[5] To our knowledge, germline or tumor specimens from this patient have not been submitted for *BMPER* mutation research testing. A *BMPER* knock-out mouse model has been reported to demonstrate a similar phenotype to that of DSD patients with craniofacial and vertebral ossification anomalies, renal abnormalities, and perinatal mortality due to thoracic insufficiency, which highlights the likely causal nature of *BMPER* mutations in the DSD syndrome.[5] The link between *BMPER* mutations in DSD and the molecular pathogenesis of Wilms tumor remains unclear, however. Signaling pathways involving the bone morphogenetic protein (BMP; a member of the transforming growth factor-beta superfamily) have been linked to the regulation of cellular proliferation, mesenchymal differentiation, and skeletal morphogenesis.[5] Earlier studies have suggested a role for BMP signaling in Wilms tumor and other renal cancers via phosphorylation of receptor-regulated SMAD proteins and via mitogen-activated protein kinase (MAPK) pathway signal transduction.[18–20] SMAD complexes accumulate in cellular cytoplasm, then translocate to the nucleus to act as transcription factors for the regulation of target gene expression.[20] The current case and genetic data from other DSD patients suggest that additional characterization of BMP signaling pathways and *BMPER* mutations may provide insight into the pathogenesis of DSD itself, as well as into DSD-associated nephroblastomatosis and Wilms tumor.

This child is the only known patient with DSD-associated Wilms tumor. The natural course of DSD-associated nephroblastomatosis and Wilms tumor pathogenesis remains unknown due to the limited life expectancy of patients with DSD. The largest case series of 16 DSD patients (reported when this patient was nine months old) notes 8 of 11 evaluated patients with radiographic or pathologic evidence of intralobar or perilobar nephroblastomatosis.[4] This patient, who survived the perinatal period due to multiple pulmonary interventions, lived long enough for his perilobar nephroblastomatosis, perhaps not surprisingly, to evolve into anaplastic Wilms tumor that proved refractory to all anti-cancer therapy utilized. Nonetheless, we were able to treat this extremely medically fragile patient with multi-modality therapy for over three years from the time of his initial nephroblastomatosis diagnosis, and he had an excellent quality of life, even while receiving palliative care. Children with DSD who survive the perinatal period should thus be serially monitored for nephroblastomatosis, as near-universal evolution of perilobar nephroblastomatosis into Wilms tumor has been reported.[15,16] DSD appears to be a Wilms tumor predisposition syndrome.

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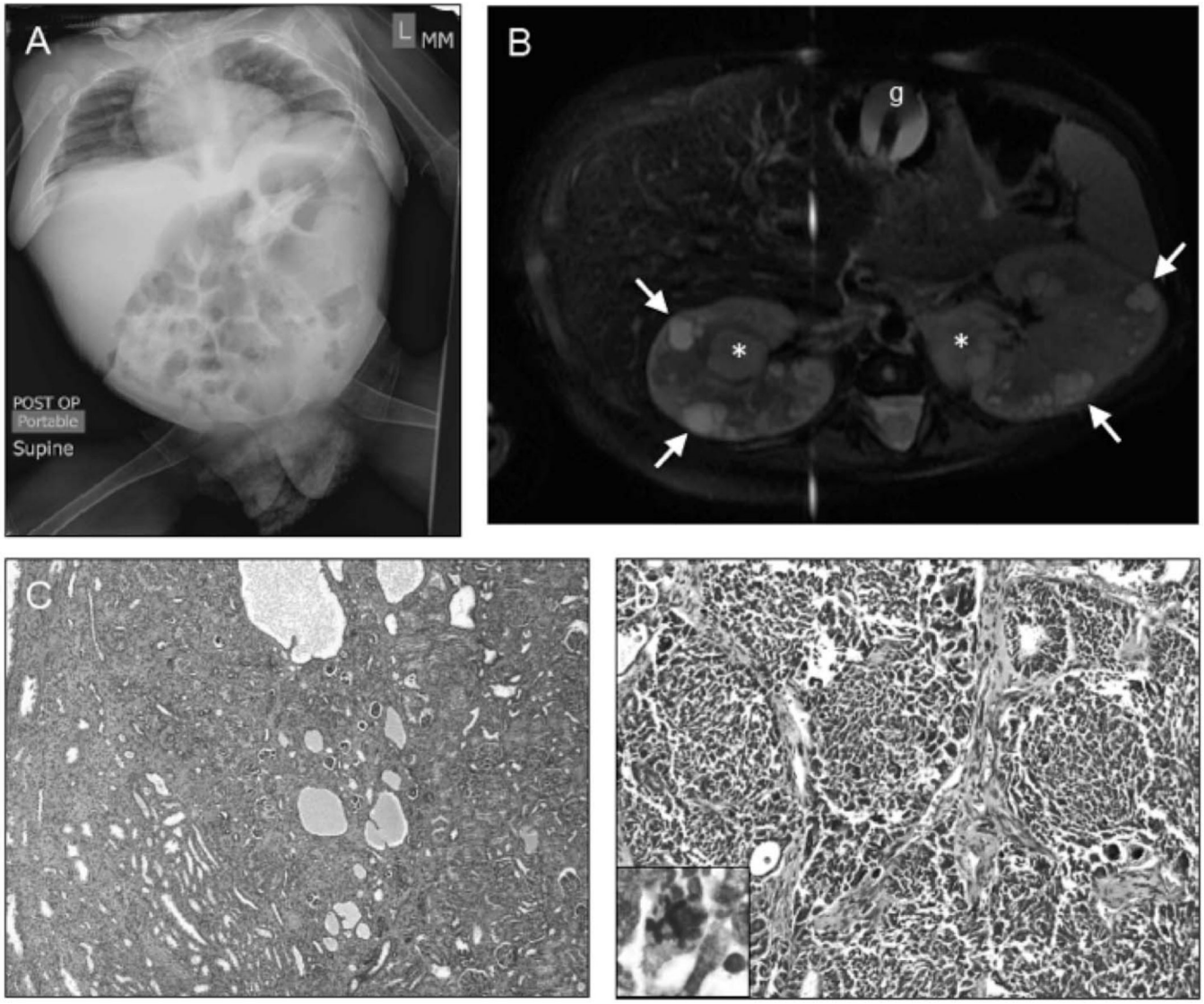

FIGURE 1.

Initial presentation of bilateral hyperplastic nephroblastomatosis and development of subsequent Wilms tumor. A, Chest x-ray demonstrates no evidence of pulmonary metastasis at diagnosis. Note the patient's bell-shaped thorax, absence of bilateral lower ribs, and sacral agenesis, which are features of diaphanospondylodysostosis. Central catheter and tracheostomy tube are in place. B, T2-weighted abdominal/pelvic magnetic resonance imaging at initial diagnosis demonstrates bilateral nephroblastomatosis (asterisks) within congenital cystic kidneys (arrows). g indicates gastrostomy tube. C, Hematoxylin and eosin (H&E) staining of initial biopsy of renal lesions demonstrates hyperplastic nephroblastomatosis and no evidence of Wilms tumor. D, H&E staining of subsequent left nephrectomy specimen after spontaneous renal hemorrhage demonstrates anaplastic Wilms tumor (×10) with abnormal mitoses (inset, ×40).

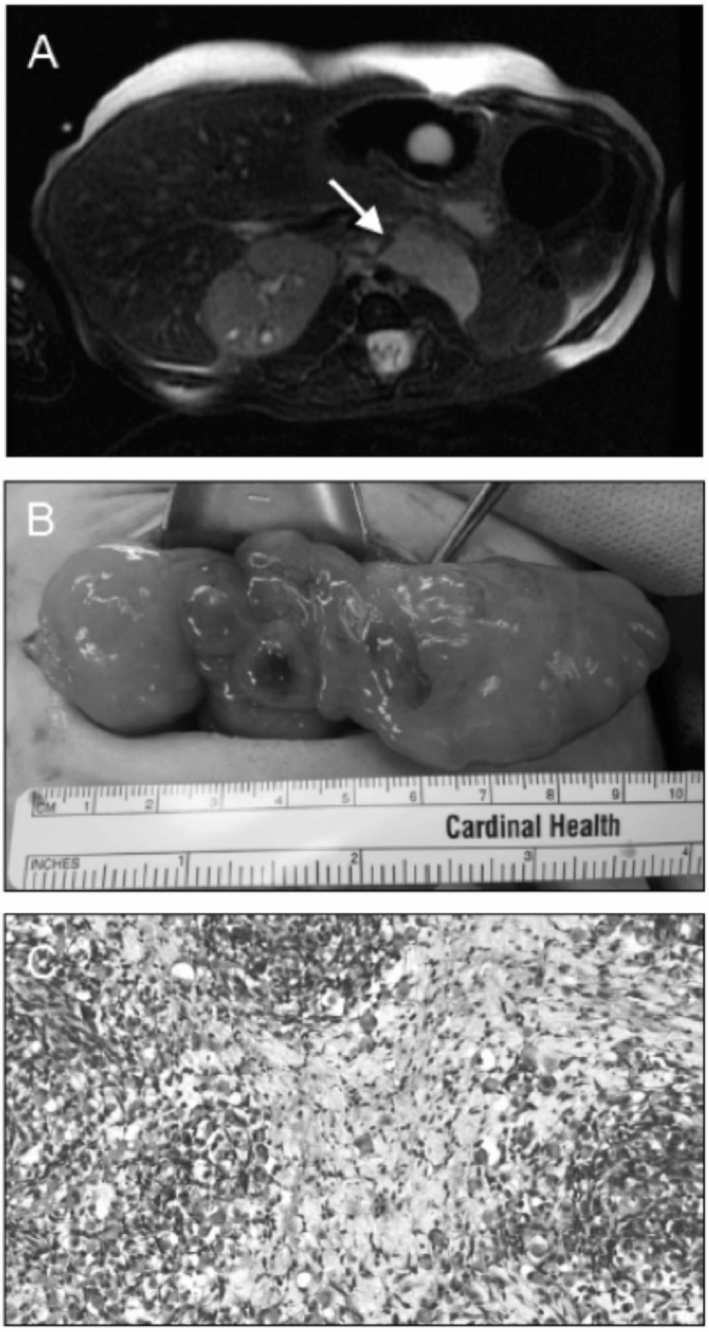

FIGURE 2.

Relapse of Wilms tumor. A, T2-weighted magnetic resonance imaging of the abdomen and pelvis demonstrates recurrent tumor originating in left nephrectomy bed (arrow). Tumor crosses midline into the right abdomen (not seen in this plane). B, Intraoperative photograph of recurrent multilobulated tumor. C, Hematoxylin and eosin staining of recurrent tumor demonstrates poorly-differentiated Wilms tumor with rhabdomyomatous features (×10).