Wilms Tumor After Orthotopic Liver Transplant in a Patient With Alagille Syndrome

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We present a case of Wilms Tumor in a patient with Alagille syndrome 10 months after liver transplant. We explore a suggested genetic connection between these 2 diseases. In children with Wilms Tumor, we propose a pathoembryologic explanation for not just the tumor, but also for the cause of associated benign ureteral and renal parenchymal aberrancies that are commonly seen in the Alagille population. We also discuss the diagnostic and therapeutic challenges that can arise in a liver transplant patient with Alagille syndrome who subsequently develops a renal mass. UROLOGY 121: 171–174, 2018. © 2018 Elsevier Inc.

Alagille syndrome was described in 1969 in a patient lacking intrahepatic bile ducts leading to cholestatic jaundice. It is estimated to occur in 1:70,000 live births[1] and is caused by mutations in the *JAG1* gene that encodes a ligand in the NOTCH receptor pathway, and is associated with facial, cardiac, ocular, and skeletal dysmorphisms.[2] Approximately 10% of children with Wilms tumor (WT) have congenital anomalies and syndromes,[3] however, there are currently just 2 reported cases of WT in patients with Alagille syndrome.[4] Unlike our patient, neither had received a liver transplant prior to developing WT.

CASE HISTORY

A male infant was born at 35 weeks gestation; prenatal ultrasound was significant for a left renal cyst. Soon after birth, he developed conjugated hyperbilirubinemia and failed to thrive. An intraoperative cholangiogram revealed a paucity of intrahepatic biliary ducts. Genetic workup revealed a *JAG1* transversion on exon 2 confirming a diagnosis of Alagille syndrome. Due to progressive liver failure, at 20 weeks of age he underwent a CMV-positive deceased-donor orthotopic liver transplant. His immunosuppression regimen included tacrolimus.

Ten months after his transplant, an US revealed a 2.8 × 1.5 cm left renal mass. Percutaneous biopsies of the mass were done for concern of post-transplant lymphoproliferative disorder (PTLD); however, these revealed foci of *WT1* and *PAX8* positive intralobar nephrogenic rests. A subsequent CT scan showed the mass to have grown to an 8.5 × 5.4 cm heterogeneous-appearing mass that occupied the majority of the left kidney (Fig. 1) with a smaller (1.0 cm) indeterminate lesion within the right kidney. Concern arose for WT given the *WT1* and *PAX8* positive nephrogenic rests seen on prior biopsies and he received 6 weeks of neoadjuvant doxorubicin, vincristine, and dactinomycin as per Children's Oncology Group protocol AREN0534.[5] The mass decreased in size after chemotherapy, but remained 7.1 × 4.3 cm (Fig. 2). The small lesion in the right kidney was stable in size when compared with prior images (Fig. 3) and was felt to be consistent with an infarct vs a stable nephrogenic rest. Because the appearance of the mass was strongly suggestive of tumor, he underwent a left radical nephrectomy with retroperitoneal lymphadenectomy. It is our institutional preference to perform a partial nephrectomy for WT, however, the large size and intrarenal nature of the tumor required radical excision. The lesion on his soon to be solitary right kidney was not biopsied nor excised due to its proximity to the transplant liver, as its wedge-shaped appearance was suggestive of an infarct and had not increased in size on serial imaging. There was no tumor spillage. Pathologic examination revealed WT with partial therapeutic effect with areas of necrosis, intralobar rests, and stromal morphology. There was no evidence of tumor in the sampled lymph nodes. Abdominal radiation therapy was not performed.

Presented at the 2017 Meeting of the Pediatric Urologic Oncology Working Group (PUOWG), Societies of Pediatric Urology Fall Congress, Montreal.

Financial Disclosure: *Jonathan C. Routh receives grant support from the NIDDK for scientific study. The remaining authors declare that they have no relevant financial interests.*

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Submitted: February 23, 2018, accepted (with revisions): May 22, 2018

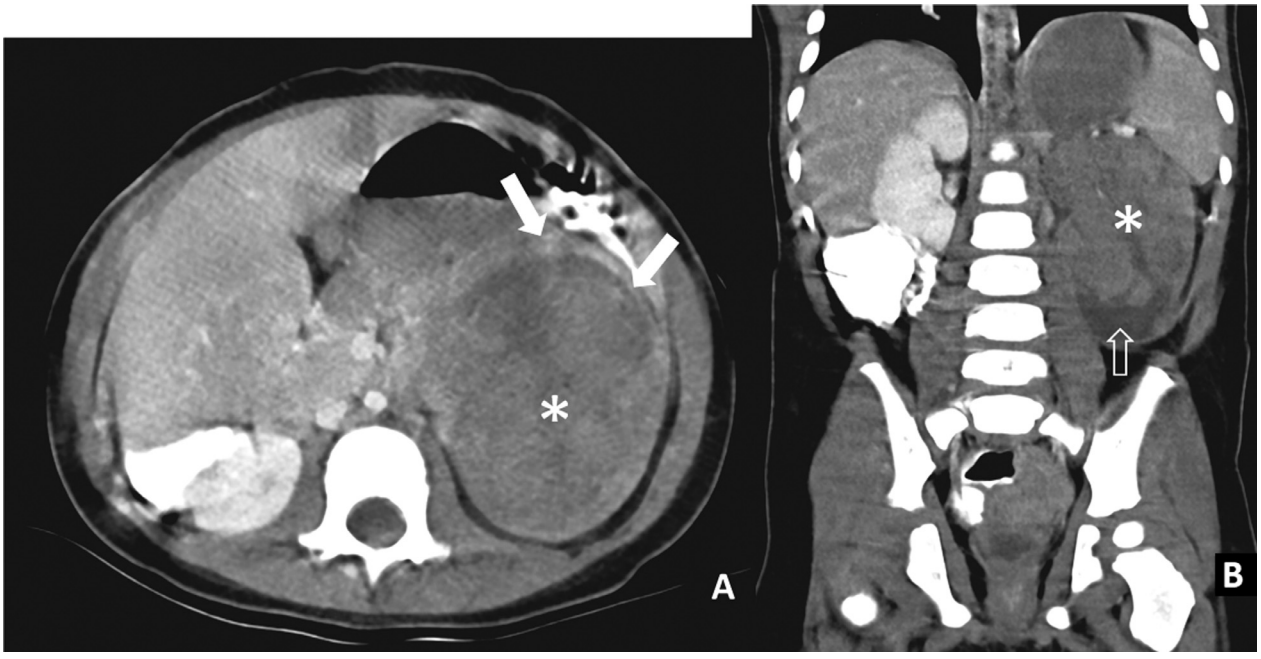

Figure 1. Computed Tomography Images at Diagnosis. (**A**) Axial images of the abdomen obtained after intravenous contrast administration demonstrate an 8.5 × 5.4 cm left renal mass (asterisk) exhibiting slight hypoattenuation compared to the surrounding renal parenchyma (solid arrows). (**B**) Coronal images reveal the heterogeneous nature of the tumor with areas of hypoattenuation (open arrow).

Over the last ten months the right renal lesion has remained stable. After surgery, he continued AREN0534 (DD4A) to complete 28 weeks of doxorubicin, vincristine, and dactinomycin given his bilaterally-predisposed unilateral WT.[5]

DISCUSSION

The first gene mutation identified in WT was *WT1*. Thereafter, links between WT and *WT1*-mutation syndromes such as WAGR, Frasier, Denys-Drash, and Beckwith-Wiedemann were established.[2,5–7] Since then,

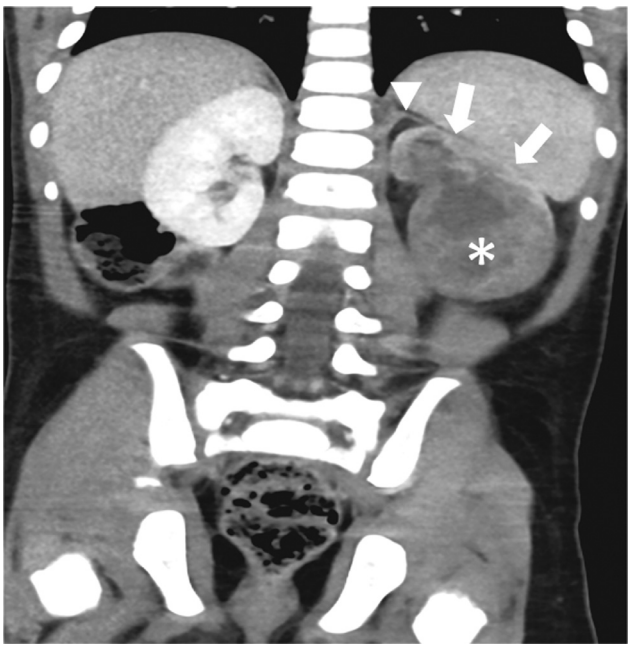

Figure 2. Postneoadjuvant chemotherapy: Coronal CT image obtained with intravenous contrast demonstrates a significant decrease in size of the left renal mass to 7.1 × 4.3 cm (asterisk). A small amount of residual renal parenchyma can be seen around the superior pole of the kidney (arrows). Normal left adrenal gland (arrow head).

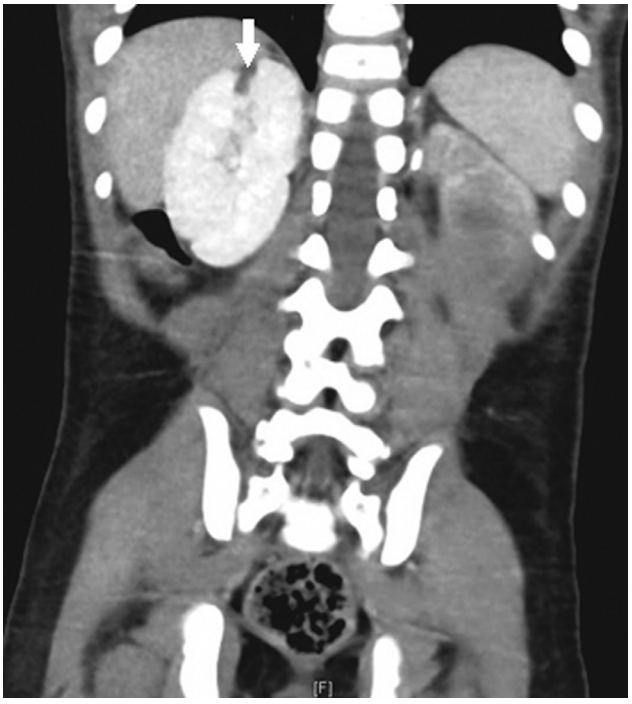

Figure 3. Postneoadjuvant chemotherapy Coronal CT image obtained with intravenous contrast shows the hypoattenuating 1.0 × 0.7 cm wedge-shaped lesion on the upper pole of the right kidney (arrow). Lesion was read as an infarct vs stable nephrogenic rest.

multiple other genes and syndromes like *BRCA2* with Fanconi anemia and Li-Fraumeni have also been implicated in WT pathogenesis.

JAG1 is a ligand in the *NOTCH* receptor signaling pathway and is found to be either partially or completely mutated in 94% of Alagille patients.[8] A 2012 study noted that among those with a *JAG1* mutation, 40% were found to have renal abnormalities.[9] In this study, renal abnormalities or dysplasia were defined as renal cysts, increased echogenicity on renal ultrasound and reduced organ size. Overall, renal dysplasia (60%) is the most common kidney abnormality in Alagille syndrome.[9] Other prominent renal findings included vesicoureteral reflux (8.2%), renal tubular acidosis (9.5%), and obstruction at the ureteropelvic or ureterovesical junctions (8.2%). WTs were not identified in any of these patients.

NOTCH2 mutations are relatively rare in Alagille cases, affecting only 0.8% of patients.[10] *NOTCH2* is found on chromosome 1p12 and is expressed in the branched ureteric bud and throughout the embryonic nephron.[10,11] *JAG1* expression is seen in the development of the early glomerulus and proximal tubule.[10] Given the close association of *JAG1* and *NOTCH2* with the ureteric bud and renal parenchyma development, this could offer a possible explanation for the increased incidence of the aforementioned benign renal and ureteral abnormalities in Alagille syndrome patients.

The JAG-NOTCH ligand/receptor pathway is involved in cell proliferation and differentiation; mutations in *JAG* or *NOTCH* genes have been reported to have oncogenic consequences.[12,13] We hypothesize that this is where the pathoembryology of Alagille syndrome and WT may intersect. *JAG1* and *NOTCH2* are intimately associated with orderly nephron development and aberrancies may cause a disorganized nephron that is histologically seen in WT. 1p deletions are seen in 18%-20% WT patients and are thought to be associated with a poorer prognosis.[3,14,15] Given these pathways, perhaps Alagille patients should be closely monitored for WT, particularly those with a *NOTCH2*(1p12) mutation.

After our patient's liver transplant, a left lower pole renal lesion was seen and concern arose for PTLD vs WT. PTLD is a life-threatening neoplasm that occurs in approximately 6% of patients after pediatric liver transplantation[16] and is commonly treated with reduced immunosuppression. We were faced with the challenging decision of whether or not to biopsy this mass. A PTLD-positive biopsy could avoid toxic chemotherapy and invasive surgery; however, if it revealed WT the biopsy itself could upstage the tumor. Understanding that 22% of Alagille patients have a GFR <90 ml/min[17] and that our patient's risk for renal insufficiency was further heightened by calcineurin immunosuppression, renal preservation was imperative. However, given the size and the intrarenal location of the mass, a radical nephrectomy was the only surgical option. Our patient's transplanted liver came from a CMV-positive donor which placed him at a higher risk for an active CMV infection which is an independent risk factor for the development of Epstein Barr Virus-related PTLD.[18] Additionally, if treating for WT, biopsy

proven or not, the patient would receive neoadjuvant chemotherapy according to the AREN0534 regimen, given his bilaterally-predisposed unilateral WT.[5] The anthracyclines used in this regimen are particularly cardiotoxic and hepatotoxic; 2 organs that are often dysfunctional in Alagille patients. Because of the potential cardiac, hepatic, and renal sequelae of initially treating for WT, we determined that a renal biopsy was in this patient's best interest. Complex clinical situations such as this require a multidisciplinary approach to address the utility of biopsy with the patient's liver transplant status, tolerance for chemotherapy, surgery, radiation, and risk for PTLD all considered.

Immunosuppressed children after a renal transplant are at increased risk of post-transplant malignancy.[19] Extrapolated to the 20%-50% of children with Alagille syndrome who eventually receive a liver transplant,[2,20,21] immunosuppression increases the risk for WT or other malignancy in a relatively vulnerable population. Children with Alagille syndrome who are immunosuppressed or may soon be immunosuppressed may benefit from serial observation with renal ultrasonagraphy.

CONCLUSION

Many patients with Alagille syndrome receive liver transplants and may be at an increased risk of malignancy. We suggest a potential pathoembyrologic link between Alagille syndrome and WT. Consideration should be given to serially monitoring immunosuppressed Alagille patients with renal ultrasounds at regular intervals.

Acknowledgment. Gary Schooler, MD from the Duke Department of Radiology, Division of Pediatric Radiology for his assistance in obtaining the figures for this report. Ashley Wietsma, MD of Duke Urology for manuscript review and editing.

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