Concomitant Wilms Tumor and Autosomal Dominant Polycystic Kidney Disease

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Abstract

Background: Concomitant Wilms tumor (WT) and autosomal dominant polycystic kidney disease (ADPKD) is exceedingly rare, presenting a diagnostic and technical challenge to pediatric surgical oncologists. The simultaneous workup and management of these disease processes is incompletely described. Procedure: We performed a retrospective analysis of patients treated at our institution with concomitant diagnoses of WT and ADPKD. We also review the literature on the underlying biology and management principles of these conditions. Results: We present three diverse cases of concomitant unilateral WT and ADPKD who underwent nephrectomy. One patient had preoperative imaging consistent with ADPKD with confirmatory testing postoperatively, one was found to have contralateral renal cysts intraoperatively with confirmatory imaging post-nephrectomy, and one was diagnosed in childhood post-nephrectomy. All patients are alive at last follow-up, and the patient with longest follow-up has progressed to end-stage kidney failure requiring transplantation and dialysis in adulthood. All patients underwent germline testing and were found to have no cancer predisposition syndrome or pathogenic or likely-pathogenic variants for WT. Conclusion: Concomitant inheritance of ADPKD and development of WT is extremely rare, and manifestations of ADPKD may not present until late childhood or adulthood. ADPKD is not a known predisposing condition for WT. When ADPKD diagnosis is made by family history, imaging, and/or genetic testing before WT diagnosis and treatment, the need for extensive preoperative characterization of cystic kidney lesions in children and increased risk of post-nephrectomy kidney failure warrant further discussion of surgical approach and peri-operative management strategies.

Introduction

Wilms tumor (WT) is the most common primary kidney malignancy in children, with an incidence of approximately 1/10,000, resulting in 500 to 550 cases per year in the United States.¹²³ A variety of syndromic and constitutional genetic alterations are associated with the development WT, including pathogenic/likely pathogenic variants (P/LPV) in WT1, a transcription factor important in the differentiation of metanephric mesenchyme.⁴ WT treatments are based on the Children’s Oncology Group (COG) and International Society of Paediatric Oncology (SIOP) protocols.⁵ The principal difference between the two is the use of upfront surgery in the COG protocols, with some exceptions, versus neoadjuvant chemotherapy and delayed nephrectomy in the SIOP protocols.⁵⁶ Additional consideration must be given to the risk of metachronous WT development and the risk of post-nephrectomy kidney failure, both of which are present to variable degrees in children with WT predisposition syndromes.
Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic inheritable kidney disease, usually secondary to germline P/LPV in \textit{PKD1} (85% of cases), \textit{PKD2} (15% of cases) or the recently identified \textit{GANAB} genes.\(^8,9\) Prevalence estimates for this condition have ranged widely from 1 in 500 to 3 in 10,000, with most estimates around 1/1,000.\(^10-12\) Disease penetrance is 100%, with one half of patients requiring renal replacement therapy by age 60 and patients with \textit{PKD1} mutations typically exhibiting relatively poor prognoses.\(^9\) The diagnosis of polycystic kidney disease relies upon imaging criteria, family history, and (if family history is negative) genetic testing.\(^13,14\) While much of the morbidity associated with ADPKD occurs in adulthood, approximately 3% of children with ADPKD have an early disease onset, and macroscopic cysts can be detected from an early age.\(^14\) In children with positive family history of ADPKD, those under the age of 15 with ultrasound evidence of one or more kidney cyst and fetuses or neonates with hyperechoic or enlarged kidneys are at high risk of having ADPKD.\(^14\) International consensus guidelines recommend that at-risk minors for ADPKD receive counselling on the risks and benefits of diagnostic testing, followed by immediate diagnostic testing if desired or regular screening for treatable disease manifestations such as proteinuria or hypertension without diagnostic testing.\(^14\)

Although polycystic kidneys have been observed in patients with WT, the simultaneous diagnosis of WT and ADPKD is rare.\(^15\) There is no known genetic interaction or syndrome that predisposes patients to both conditions. The possible accelerated risk of long-term kidney failure due to ADPKD after nephrectomy from loss of kidney parenchyma, as well as the need for extensive preoperative characterization of cystic kidney lesions in children, makes the timing and nature of treatments for these patients complex. In this manuscript, we present three cases of concomitant WT and ADPKD who underwent nephrectomy at our institution (Table 1) and provide a discussion of the pertinent management principles and biological underpinnings of these diseases.

**Case Presentations**

**Case 1**

A 2-year-old female presented with intermittent hematuria. On ultrasound, she was found to have a right kidney mass with a maximum diameter of six centimeters. A computed tomography (CT) scan was obtained and showed a simple cyst in the inferior pole of the right kidney and numerous tiny cysts scattered throughout the left kidney. She had a family history of ADPKD in her father, paternal uncle, and paternal grandfather. The father had normal kidney function and the paternal grandfather had recently undergone successful kidney transplantation. Preoperative magnetic resonance imaging (MRI), performed to further evaluate the cysts for solid components, revealed scattered, simple, fluid-filled cysts (Figure 1A & 1B). Review of the imaging with an experienced radiologist yielded no concerns for bilateral WT (BWT) or nephrogenic rests. The patient underwent successful transabdominal right radical nephrectomy and lymph node sampling without complication or tumor spillage. Several small fluid-filled cysts were noted in the adjacent normal right kidney parenchyma intraoperatively (Figure 1C). Final pathology from the right nephroureterectomy was reported as triphasic WT with involvement of the kidney sinus tissue. Intralobar nephrogenic rests were present. The tumor was stage II and no lymph node metastases were seen. Chest CT scan demonstrated no metastatic nodules. Germline testing of 115 cancer-related genes did not identify any genetic predisposition syndrome. She had normal kidney function post-operatively and received adjuvant vincristine and dactinomycin. Further ADPKD-specific genetic testing after surgery demonstrated a germline P/LPV of \textit{PKD1}, p.C1295T. At the time of publication, this patient is more than two years off adjuvant therapy with normal blood pressure and kidney function.

**Case 2**

A 5-year-old male with beta-thalassemia trait presented with a two-month history of intermittent abdominal pain, vomiting, and a palpable right-sided abdominal mass. Preoperative ultrasound demonstrated a heterogeneous solid and cystic mass in the right kidney measuring 9 x 11 x 14 cm with a normal-appearing left kidney. He underwent right radical nephrectomy with lymph node sampling. Due to local tumor spillage intraoperatively, his tumor was stage III. Final pathology was reported as favorable histology WT. The pa-
tient received adjuvant chemotherapy with vincristine, dactinomycin and doxorubicin, and whole abdomen radiation therapy (AP-PA; 12 Gy; 4 MeV). Small subcentimeter hypodense areas of thought to be cysts or metachronous WT were noted in the left kidney on abdominal CT one-month post-nephrectomy, and these remained stable in size and number over the following 2 years on serial CTs. He underwent repair of a right-sided scrotal hydrocele and urethral meatoplasty at age 12 years and was diagnosed with autism spectrum disorder in adolescence. He was evaluated by a local nephrologist at 15 years for hypertension. Due to progressively worsening kidney function and positive family history of ADPKD in his father diagnosed at age 43 and paternal grandmother diagnosed in her 60s, ADPKD genetic testing was eventually performed and confirmed a P/LPV in the PKD2 gene, p.G1365A. Notably, both the patient’s father and paternal grandmother were diagnosed with ADPKD several years after the patient’s WT diagnosis. He underwent arteriovenous fistula creation at age 20 years for chronic kidney failure. After six years of hemodialysis, he underwent kidney transplantation at age 25. He then underwent native left nephrectomy less than two years later at age 27 for a painful left cystic kidney and final pathology was reported as benign cystic changes. After experiencing acute graft rejection, he restarted hemodialysis and is awaiting a second kidney transplant at the time of this publication. Follow-up genetics counselling at our institution at age 32 led to targeted germline genetic testing of 191 cancer-related genes which demonstrated no P/LPV, suggesting an underlying cancer predisposition syndrome is unlikely.

Case 3
A 5-year-old female with a three-year history of syncopal episodes presented with left flank pain and fever. Ultrasound demonstrated a left-sided kidney tumor. CT scan demonstrated a large heterogeneously enhancing mass in the mid-to-lower pole of the left kidney measuring up to 7.5 cm and a second mass in the upper pole of the left kidney measuring up to 4.0 cm in diameter (Figure 2A-D). The right kidney was normal. Chest CT demonstrated no pulmonary metastases. She underwent left radical nephrectomy with lymph node sampling, and intraoperative ultrasound of the right kidney demonstrated no solid masses but several cysts. Final pathology demonstrated multifocal WT; the larger mass was found to have diffuse anaplasia with perilobar nephrogenic rests and the smaller upper pole mass was favorable histology. Local stage was stage III due to the presence of tumor in one of two kidney hilar lymph nodes. She received adjuvant radiation therapy to the whole abdomen (AP – PA; 6 MV; 10.5 Gy) and a boost to the left flank (AP – PA; 6 MV; 9.5 Gy) as well as adjuvant chemotherapy for eight months with vincristine, cyclophosphamide, doxorubicin and etoposide per the AREN0321 UH-1 protocol.\textsuperscript{16} Family history was significant for her paternal grandmother, four paternal great uncles and one paternal great aunt with ADPKD. Clinical next generation sequencing (NGS) of her tumor identified P/LPVs MYCN p.P44L, TP53 p.C176G, and DICER1 p.R821H in the anaplastic foci. The smaller mass with favorable histology was negative for these alterations and no additional P/LPVs were identified. However, germline NGS of 64 cancer-predisposing genes, including TP53 and DICER1 demonstrated no P/LPVs. Her most recent ultrasound at age 11 demonstrated numerous right kidney cysts measuring up to 1.4 cm in diameter (Figure 2E & 2F). She had follow-up with nephrology most recently at age 13 years and was noted to have hypertension and chronic kidney disease stage 2 but has not yet undergone formal genetic testing for ADPKD, which is anticipated within a year of this publication.

Discussion

Genetics of WT and ADPKD
ADPKD and WT are distinct clinical diagnoses with known, non-interacting genetic drivers. Multidisciplinary care for patients with both conditions is essential to optimize long-term outcomes. PKD1 and PKD2 are the most commonly mutated genes in the pathogenesis of ADPKD, as mentioned previously. These two genes are located on chromosomes 16p13.3 and 4q21, respectively.\textsuperscript{13} PKD1 encodes for Polycystin 1, and PKD2 encodes for Polycystin 2. These proteins are involved in numerous structures and functions, including primary cilia, tight junctions, cell adhesion, and calcium regulation.\textsuperscript{17} Cystogenesis in ADPKD has been postulated to be due to multiple interacting mechanisms, including a somatic “second-hit” model (due to the occurrence of localized cystogenesis despite ubiquitous expression.
of inherited mutations throughout the kidney) and that of reaching below a critical threshold of PKD gene activity triggering pathways of fibrosis, cellular proliferation and fluid secretion.\textsuperscript{17–19} This could contribute to the heterogenous clinical presentations demonstrated in the cases described in this series. This is additionally postulated to contribute to the intrafamilial variation in ADPKD phenotypes and penetrance.

A variety of syndromic and constitutional genetic alterations are associated with the development WT, including in the transcription factor \textit{WT1} at 11p13 expressed during condensation of the metanephric mesenchyme in kidney development.\textsuperscript{20} The kidney parenchyma surrounding WT can exhibit mosaic alterations present in the adjacent WT, but absent in tissues of different embryonic lineages, such as the kidney pelvis.\textsuperscript{21} This phenomenon of cancer arising within a milieu of histologically normal tissue that has undergone aberrant clonal expansion during fetal development appears unique to pediatric cancer development when contrasted with the clonal expansion of cells with somatic mutations seen in malignancies of adulthood, such as with the adenoma-carcinoma sequence of colorectal cancer.\textsuperscript{22}

There has been some investigation into the genetic interaction of WT with \textit{PKD1} given the importance of WT1 on the differentiation of kidney parenchyma. In a study by Münch et al, knockdown of murine \textit{WT1} decreased \textit{Pkd1} mRNA as well as expression of the \textit{PC1} protein.\textsuperscript{23} However, given the overwhelming number of cases of ADPKD that arise without WT, we speculate the simultaneous development of these diseases is most likely to be coincidental. Given the general incidences of these diseases, the independent development of WT and inheritance of ADPKD could be estimated at \(1/10,000 \times 1/1,000 = 1/10,000,000\). According to our review of the literature, this publication appears to be only the second report of simultaneous WT and ADPKD, with the only preceding publication describing a patient diagnosed with ADPKD in infancy and later diagnosed with WT at age 2 years incidentally via MRI performed for liver pathology screening.\textsuperscript{24}

\textbf{Management of WT and ADPKD}

For those with known ADPKD at the time of diagnosis of WT, there is an added layer of complexity to perioperative management. First, extensive preoperative characterization of cystic kidney lesions in children is imperative. In Case 1, bilateral kidney cysts were visible during the preoperative workup. This prompted careful review of the CT scan with a radiologist experienced in pediatric solid tumors, followed by an MRI to further characterize the cystic structures in the kidney parenchyma. Subtle solid tumor components must be characterized, given differences in treatment protocols for BWT,\textsuperscript{25–27} and simple cysts must be differentiated from cyst structures of other disease entities such as cystic WT, WT in the setting of multicystic dysplastic kidney,\textsuperscript{28,29} cystic partially differentiated nephroblastosomas,\textsuperscript{30–32} and benign cystic nephromas.\textsuperscript{32,33} Atypical cyst development in ADPKD in children can masquerade as tumor components as well.\textsuperscript{34,35} If there is diagnostic uncertainty, high resolution MRI can be used to distinguish complex cystic structures from benign and malignant neoplasms due to its superior soft tissue resolution and lack of ionizing radiation (of particular concern in children).\textsuperscript{36,37} Contrast enhanced ultrasound is also useful to confirm the cystic nature of lesions and to identify solid components. It has the added benefits of no ionizing radiation, no need for sedation and, perhaps most importantly in this patient population, unlike other contrast agents, ultrasound contrast agents are not metabolized by the kidney and have no nephrotoxic effect.\textsuperscript{38,39} Simple cysts have reported prevalences of 0.2–2\% in childhood and increase with age, and conservative management with serial ultrasounds is recommended for patients with solitary, asymptomatic cysts without family history of ADPKD.\textsuperscript{40,41} In these cases, serial ultrasounds in the patient should evaluate for development of multiple or complex cysts, and screening of parents with ultrasound is also recommended. The presence of multiple simple cysts in children with a known family history of ADPKD is virtually diagnostic of ADPKD, and patients with multiple cysts without a family history of ADPKD should likewise be further investigated for ADPKD or other cystic nephropathies.\textsuperscript{14,40,42}

A second general principle in management of WT is that risk of kidney failure must be balanced against oncologic risk. Some molecular abnormalities carry a high rate of WT risk, including metachronous bilateral tumors.\textsuperscript{43} The COG study AREN0534 encompassed three arms which defined patients benefiting from neo-adjuvant chemotherapy with a goal of maximizing kidney parenchyma.\textsuperscript{44} One arm included patients with predisposition syndromes with high risk of metachronous WT development, including patients with WAGR
syndrome, Denys-Drash syndrome, Frasier syndrome, Beckwith-Wiedemann Syndrome (BWS), idiopathic hemihypertrophy (IHH), and Simpson-Golabi-Behmel syndrome. For these patients, nephron-sparing surgery (NSS) following neoadjuvant chemotherapy is warranted when unilateral WT (UWT) is present due to the risk of development of WT in the contralateral kidney and variable risks of developing renal failure. However, there is ongoing debate about the role of NSS in patients with BWS and IHH who present with UWT given their relatively lower risk of developing kidney failure compared to other predisposition syndromes, high prevalence of perilobar nephrogenic rests in the remnant kidney, and low absolute risk of contralateral WT recurrence. Regardless, WT in BWS and IHH are also treated according to AREN0534 study protocols currently. Importantly, rates of microscopic positive margins and complications are higher in NSS than in radical nephroureterectomy.

Conversely, ADPKD has no known risk of metachronous WT development, though studies of surgical kidney specimens in patients with ADPKD have revealed rates of renal cell carcinoma as high as 12%. Several case series have demonstrated pre-cancerous structures in ADPKD specimens, as well as increased rates in patients with ADPKD on hemodialysis compared to non-ADPKD patients receiving hemodialysis. However, the biological basis of these relationships has not been defined. Further, it is not currently known whether individuals with ADPKD have an increased risk of other childhood malignancies, and cases of these co-occurrences have been infrequently reported.

As mentioned previously, the natural history of ADPKD is generally of universal progression towards end-stage kidney failure, albeit with significant variability between genetic mutations and within affected families. There is some evidence that nephrectomy in patients with ADPKD and normal kidney function may accelerate development of kidney failure. Therefore, hypothesized earlier progression of kidney failure following total nephrectomy compared with NSS should be considered, and aggressive blood pressure control with angiotensin converting enzyme (ACE) inhibitor and/or angiotensin 2 receptor blocker medications postoperatively is likely warranted to mitigate loss of kidney mass regardless of surgical approach.

On the other hand, while most patients with WT receive chemotherapy including vincristine and dactinomycin with or without doxorubicin, adjuvant nephrotoxic chemotherapy such as ifosfamide and platinum-based drugs and whole abdomen radiation therapy have been associated with increased risks of congestive heart failure, kidney failure, and hypertension in long-term follow up of patients with WT. Given the increased oncologic risk of NSS with no known risk of metachronous contralateral WT development in patients with WT and ADPKD, the benefits of total nephrectomy may outweigh the risks of accelerating kidney failure in these patients, but surgical approach should be discussed in a multidisciplinary, case-by-case manner.

Conclusions
The concomitant inheritance of ADPKD and development of WT is extremely rare and likely coincidental. Extensive preoperative characterization of cystic kidney lesions in children is imperative when ADPKD is diagnosed preoperatively, and MRI can be used to concurrently assess the primary renal tumor(s) and identify renal cysts. These patients are at especially high risk of accelerated kidney failure following surgery and should be regularly evaluated for treatable manifestations of ADPKD. Given the increased oncologic risk of NSS with no known predisposition for WT development in ADPKD, the benefits of total nephrectomy for patients with WT and ADPKD may outweigh the risks of accelerated kidney failure, although surgical approach and postoperative care should be discussed in a multidisciplinary case-by-case fashion.

Conflicts of Interest Statement: The authors declare no financial disclosures or conflicts of interest related to the research described in this manuscript.

Ethics Statement: A waiver of informed consent was obtained for this study as it was deemed exempt by IRB approval.

References


**Tables and Figures**

**Table 1.** Summarized cases of concomitant Wilms tumor (WT) and autosomal dominant polycystic kidney disease (ADPKD) in children

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<tr>
<th>Case #</th>
<th>Age at WT diagnosis</th>
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**Figure 1.** Images from Case 1.  

**A & B:** Representative axial images from the preoperative T1-weighted abdominal MRI with gadolinium contrast in Case 1.  

**A:** Large right kidney mass with clear involvement and compression of the collecting system (long solid white arrow).  

**B:** Heterogeneous solid (straight solid arrow) and cystic (curved solid arrow) components of the right kidney mass and simple cysts in the left kidney (dashed white arrows).  

**C:** Intraoperative photograph during the right radical nephroureterectomy; the superior DeBakey forceps point to the tumor, while the inferior forceps point to a cyst, visible in the larger circle of perinephric fat that has been cleaned off of the normal kidney for inspection.
**Figure 2.** Images from Case 3. **A-D:** Representative preoperative computed tomography (CT) images with red outlines highlighting the left kidney. **A & B:** Coronal plane images demonstrating heterogeneous masses in the upper and lower poles of the left kidney with a normal right kidney. **C & D:** Sagittal plane images. **E & F:** Representative images of follow-up right kidney ultrasound performed at age 11 (5 years after surgery), demonstrating multiple simple cysts. **E:** Axial plane image demonstrates the largest cyst measuring 1.44 cm diameter (measurement cursors are on the cyst). Other similar cysts were seen elsewhere in the kidney. **F:** Sagittal plane image (patient’s head toward the left, liver anterior and superior to the kidney) demonstrates the largest cyst in the lower pole (arrow).