

**PEDIATRIC UROLOGY CASE REPORTS**

ISSN 2148-2969

<http://www.pediatricurologycasereports.com>**Cystic nephroma with renal vein thrombus in a child with DICER1 mutation:
A case report****Erin Choi¹, Erin K. Barr², Viviane Mamlok³, Cynthia Smith⁴, Matthew Timberlake⁴**¹Texas Tech University Health Sciences Center, Lubbock, TX, USA²Department of Pediatrics, Texas Tech University Health Sciences Center, Lubbock, TX, USA³Department of Pathology, Texas Tech University Health Sciences Center, Lubbock, TX, USA⁴Department of Urology, Texas Tech University Health Sciences Center, Lubbock, TX, USA**ABSTRACT**

Venous tumor thrombus is a known manifestation of Wilms' tumors in a minority of cases but has not been previously described in association with cystic nephroma. We report an original case of a histologically-benign cystic nephroma presenting with venous tumor thrombus extending to the inferior vena cava. The tumor thrombus was not detected by preoperative Doppler ultrasound. The patient was successfully treated with radical nephrectomy, tumor thrombectomy, and IVC closure. Postoperatively, the patient underwent genetic testing which revealed a DICER1 mutation—known to predispose affected individuals to a variety of benign and malignant tumors—and requires intensive surveillance for associated conditions.

Key Words: Nephroma, tumor thrombus, thrombectomy, DICER1 mutation, cancer predisposition syndrome.

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Received: 2020-08-26 / Revisions: 2020-10-14

Accepted: 2020-10-25 / Publication Date: 2020-11-01

Introduction

Cystic nephroma (CN) or multilocular cystic nephroma (MLCN) is a benign renal tumor characterized histologically by simple epithelial lined cysts, ovarian-like stroma, and fibrotic septations [1,2]. CN classically presents in a bimodal age distribution including infants/young children and middle-aged females [2,3].

Pediatric CN is associated with mutations in the DICER1 gene [4]. The consequent DICER1 syndrome is a cancer predisposition syndrome, increasing the risk of benign and malignant tumors of the lung, kidney, female reproductive tract, gastrointestinal tract, central nervous system and thyroid in affected individuals [5-7]. Venous tumor thrombus has previously been associated with Wilms' tumors, but has yet to be described in a patient with CN. We report a novel presentation of CN with venous tumor thrombus in a child subsequently found to have a DICER1 mutation.

Case report

A 2-year-old girl presented with a firm right sided abdominal mass. She had no associated fever, hematuria, or abdominal pain. There was no associated hemihypertrophy or macroglossia on physical exam and no history of renal insufficiency or urinary tract infection. Both pediatric urology and oncology were involved in the case. Computerized tomography (CT) scan revealed a 12 x 10 x 7 cm multicystic right renal mass with enhancing septations (Fig. 1A, B).

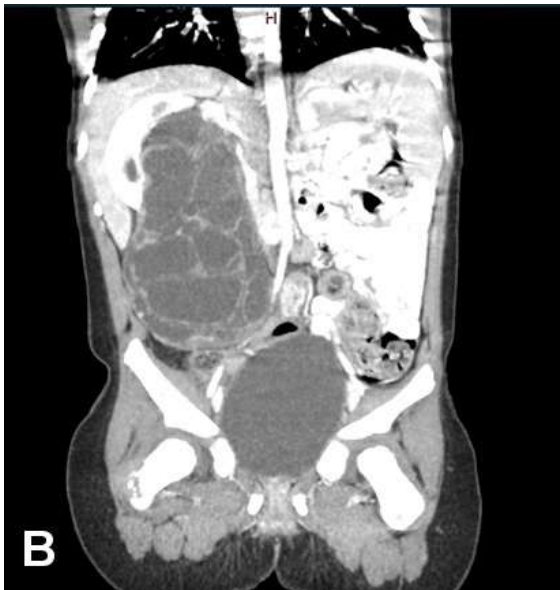


Fig. 1. A. Axial CT image of right centrally-located, cystic renal mass. **B.** Coronal CT image of right cystic renal mass draping inferiorly over right iliac vessels.

The left kidney appeared normal. Chest CT revealed no evidence of pulmonary metastasis or masses. Duplex ultrasound of the abdomen was obtained to evaluate for a tumor thrombus. A patent right renal vein and inferior vena cava (IVC) were noted (Fig. 2).

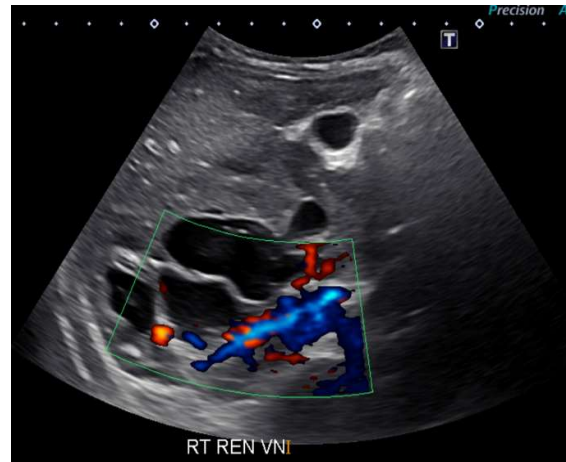


Fig. 2. Doppler ultrasound showing patent renal vein without thrombus. Intraoperatively, this was found to be superior to a second renal vein distended by thrombus.

A differential diagnosis of cystic Wilms' tumor versus CN was considered. Given the large size and centralized location, right radical nephrectomy was recommended. In the operating room, a vertical midline incision was utilized for exposure. The mass was well-encapsulated, extending inferiorly into the pelvis and draping over the iliac vessels. The right renal artery and vein were identified and sequentially ligated. This vein was uninvolved by tumor thrombus. The remainder of the mass and kidney were mobilized uneventfully. However, there was a remaining medial attachment which, at first, appeared to be a knuckle of tumor adherent to the inferior vena cava. Further dissection revealed this to be a second renal vein, distended by tumor thrombus. Given this finding, the IVC was

further exposed to allow proximal and distal control with Rimmel clamps, and the contralateral renal vein was encircled and clamped. A 5cm veinotomy was made in the IVC to allow a wide margin around the ostium of the involved right renal vein. The kidney, involved vein, and wide margin of IVC were removed en-bloc. The resection margins were grossly normal. The vena cava was then closed in conjunction with cardiovascular surgery. The IVC margins were negative. Retroperitoneal lymph node sampling was performed, which was negative for malignancy. There was no evidence of additional disease within the abdomen.

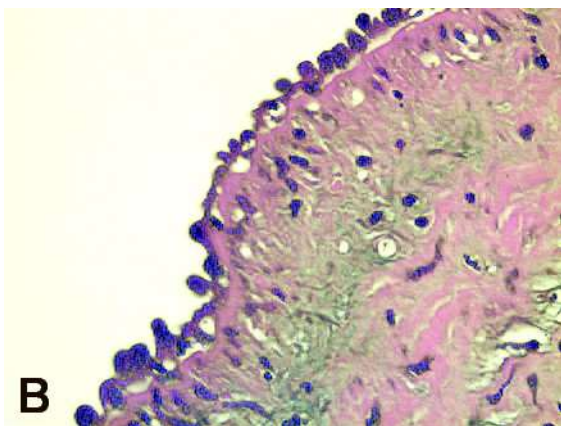
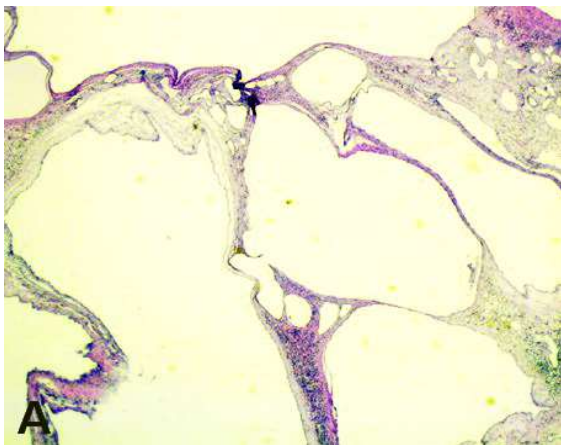


Fig. 3. A. Final histology showing cysts lined with flattened cells consistent with cystic nephroma (CN). **B.** Final histology showing cyst lining with hobnail cells.

The final specimen measured 9 x 9 x 4.5cm with multiple cysts of varying size. Cysts were lined by delicate, near translucent septa without solid areas and contained a clear, straw colored fluid. Microscopic examination showed that the epithelium lining the cysts appeared flattened with some hobnail features (Fig. 3A, B). The septa were hypocellular with some mixed mononuclear inflammatory infiltrate. There were no blastemal or embryonal elements. The final pathological diagnosis was a CN. The patient had a quick and uneventful postoperative recovery. Given the significant association of pediatric CN tumors with *DICER1* mutations, referral to a genetic counsellor with pediatric oncology follow-up was scheduled. The patient was ultimately found to be positive for a *DICER1* germline mutation. In accordance with consensus guidelines for *DICER1* screening, the patient underwent repeat chest CT and abdominal ultrasound 3 months postoperatively, which were negative for recurrent or synchronous primary malignancy [7].

Discussion

Wilms' tumor is known to be associated with venous tumor thrombus in 4-11% of cases [8-10]. To our knowledge, this is the first reported case of a venous thrombus in the setting of histologically-benign CN. Previous reports have described infiltrative behavior exhibited by CN neoplasms. Bouhafis *et al* and Kural *et al* reported parenchymally-originating CN which invaginated into the renal pelvis—in one case extending through a calyx [11,12]. Ureteral involvement through a similar mechanism has also been described [13].

Cystic renal neoplasms in children may exist on a continuum of oncologic aggressiveness. The differential diagnosis includes the benign CN and the malignant cystic nephroblastoma, or

cystic Wilms' tumor. However, intermediate forms have been described. Joshi and Beckwith proposed the term cystic partially differentiated nephroblastoma (CPDN) to describe cystic lesions lacking nodular solid regions, in which blastemal or other embryonal cells are present in the septa of the cysts [14]. CPDN may show aggressive behavior and has a tendency for recurrence after surgery [15]. In our case, blastemal or embryonal elements were absent on final pathology.

Prognosis for CN is very good with surgical treatment. Radical nephrectomy remains the most common surgical treatment for CN based on the inherent difficulty in differentiating CN from cystic Wilms' tumor radiographically. Although nephron sparing surgery has been described in select cases, [16] this was not a feasible option in our case given the large size of the mass and possibility of malignancy.

Diagnosis of a tumor thrombus relies mostly on preoperative imaging including duplex ultrasonography, CT and/or magnetic resonance imaging (MRI). In this case, preoperative duplex ultrasound was falsely-negative due in part to the presence of a second uninvolved renal vein. MRI with venography may have helped raise preoperative suspicion for tumor thrombus in this case. McDonald *et al* described three patients with IVC or renal vein tumor thrombus that was detected via MRI and CT, but was missed on the initial ultrasound [17]. Nonetheless, surgeons treating solid or cystic renal masses in children should evaluate for venous involvement intraoperatively, even in the setting of negative preoperative imaging. DICER1 germline mutations have been detected in the majority of pediatric-onset CN cases, and are thought to be a major genetic event in their development [4,5]. In contrast, the mutation is rarely detected in adult-onset CN, suggesting that pediatric and adult CN may

be distinct entities [18]. The DICER1 gene is a RNase endonuclease involved in the production of microRNAs, which ultimately regulate gene expression [5]. DICER1 mutations are largely inherited in an autosomal dominant pattern, with a small percentage occurring de novo [7]. The penetrance is modest, and it has a variable phenotype, the mechanisms of which are not completely understood at this time [7]. Germline DICER1 mutations can predispose to a variety of benign and malignant conditions, for which early diagnosis may significantly impact outcomes [5-7,19]. Bueno *et al* retrospectively analyzed imaging studies performed on children with known germline DICER1 mutations. They described malignant neoplasms in 68.8% of patients and benign neoplasms in 37.5% of patients, highlighting the need for early surveillance in DICER1 patients [19]. The diagnosis of CN in a pediatric patient is considered a major indication for DICER1 testing, and patients with confirmed mutations should be referred for genetic counseling. Schultz *et al* published consensus guidelines for testing, surveillance, and treatment for children with DICER1 mutations in 2018 [7].

The patient in this case is being followed regularly by pediatric oncology and a pediatric genetic counsellor to ensure that she receives appropriate surveillance. Genetic testing for members of the patient's family has been discussed, although there does not appear to be any family history of other cancers or DICER1 associated conditions per family report.

Conclusions

Like Wilms' tumor, histologically-benign CN can be associated with significant venous tumor thrombus. Surgeons treating solid or cystic renal masses in children should evaluate for venous involvement intraoperatively, even in

the setting of negative preoperative imaging. Given the strong association between pediatric CN and DICER1 mutations, infants and children with CN should be referred to a genetic counsellor and/or pediatric oncology team in order to test for this cancer-predisposing germline mutation.

Compliance with ethical statements

Conflicts of Interest: None.

Financial disclosure: None.

Consent: Patient confidentiality is maintained and written consent for the publication of patient details and clinical pictures in this journal has been obtained from the patient's parents or closest relative and can be given as required.

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