# Case – Bilateral and recurrent pediatric cystic nephroma associated with DICER1 mutation

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## Introduction

Pathogenic variation in DICER1 predisposes to a variety of benign and malignant neoplasms, including pleuropulmonary blastoma (PPB) and cystic nephroma (CN). Other rare tumors that can be seen include Sertoli-Leydig cell, Wilms, thyroid cancer, and certain childhood brain tumors. More recently, anaplastic sarcoma of the kidney (ASK) has also been described.[1,2] DICER1 pathogenic variation is inherited in an autosomal-dominant fashion with low to reduced penetrance (15%). With this case report, we review the current literature on this rare syndrome, with a focus on urological concerns.

## Case presentation

The patient is a nine-year-old boy who has been followed since birth as a DICER1 mutation carrier. His family history revealed a maternal cousin with a pituitary blastoma at eight months of age. That cousin, his mother, our patient, and his mother, were all found to be all carriers of the DICER1 mutation c.2379T>G [p.Y793X]. During his recommended followup, two lesions were discovered at 13 months old: one 38x28x34 mm in the right upper pulmonary lobe and a 41x34x36 mm lesion between the middle and upper pole of the left kidney. First, a right lobectomy was done, and the pathology revealed a type I PPB. One month later, a left partial nephrectomy was performed. The pathologist confirmed a CN with negative margins. The patient received a 40-week protocol of adjuvant chemotherapy for his type I PPB (vincristine, dactinomycin and cyclophosphamide).

After seven years of followup, the patient developed a new 27x30x32 mm multicystic lesion on the inferior pole of the contralateral right kidney. A second partial nephrectomy was done in August 2019. The pathology again showed a CN with negative margins. At his first postoperative followup, two months later, a new third renal lesion was identified. A 12 mm simple cyst lesion on the superior pole of the right kidney was found on ultrasound (US). At the three-month followup, the cyst had progressed to 16 mm and had more complex features with small septations. Another US was obtained two months later and showed significant growth of the lesion, now measuring 24x24x27 mm (Fig. 1).

After a discussion with the family and the multidisciplinary team, including members of the DICER1 International PPB/DICER1 Registry, the decision was made to resect the lesion. Despite the risk of fibrosis due to multiple interventions, we elected to perform a nephron-sparing surgery, with minimal morbidity, while avoiding malignant transformation. He underwent an uneventful right partial nephrectomy (enucleation type resection). He was discharged on postoperative day two, and his creatinine remained normal to his baseline. The pathology review showed an unusual CN with negative margins. The cysts showed cuboidal lining epithelium with frequent hobnailing. Cystic septa are generally hypocellular and fibrous, but focally showed layers of immatures subepithelial cells, and made this pathology similar to type-1 PPB (Fig. 2).

The institutional review board approved the study with fully informed parental consent and minor assent for the use of tumor material for biological studies.

## Discussion

Germline pathogenic DICER1 variation predisposes to a variety of cancers, including PPB, Sertoli-Leydig cell tumor, ASK, and childhood brain tumours, as well as dysplasia and benign conditions, such as thyroid nodules. Some benign conditions, such as cystic nephroma, have a risk of malignant transformation.[3,4]

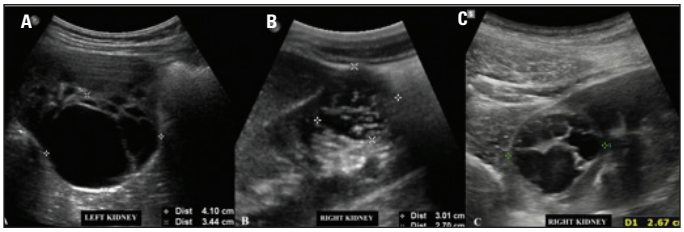


***Fig. 1.*** Cystic nephromas in DICER-1 patient. ***(A)*** A first lesion in the middle pole of the left kidney was resected in 2012. ***(B)*** A second cystic nephroma was resected in 2019 in the right kidney. (lower pole). (C) A third cystic mass resected in April 2020, which appeared to be an unusual cystic nephroma.

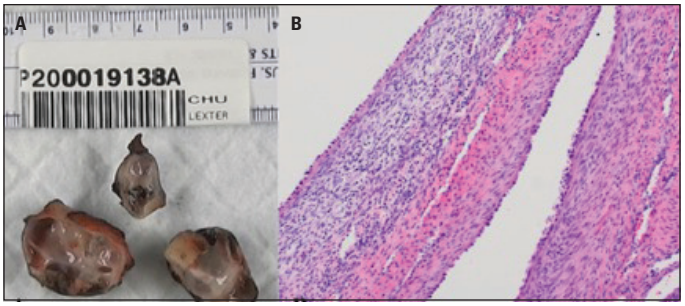


***Fig. 2.*** Third cystic lesion resected: unusual cystic nephroma. ***(A)*** Macroscopic pathology (multicystic multilocular lesion with thin septa and translucent content). ***(B)*** Microscopic pathology (cuboidal lining epithelium with frequent hobnailing).

Mutations in the DICER1 gene affect RNA expression.[5] As postulated by the two-hit hypothesis, tumors appear because one copy of the DICER1 gene is affected by a predisposing germline mutation (usually inherited in an autosomal-dominant fashion, although 10–20% of mutations are sporadic), and the other copy is affected by an acquired, somatic, tumor-specific mutation.[4]

In the U.S., approximately one in 10 600 people carries a pathogenic variant of the mutation, but it is estimated that only 20% of carriers will develop a neoplasm by 50 years of age.[4,6,7] Approximately 70% of PPBs and pediatric CNs are attributable to pathogenic DICER1 mutations.[8] Genetic counselling and consideration of testing are recommended for children and relatives of individuals with DICER1 pathogenic variation. Surveillance recommendations are available and include chest, thyroid, and abdominal imaging, in addition to individual, family, and provider education.[9,10]

The actual surveillance recommendations for kidney imaging of a patient with DICER1 mutation is an US every six months for the first eight years of life, and every year until 12 years old,[8,10,11] although the clinical utility and cost-effectiveness of this surveillance strategy has not been formally studied yet. To date, the literature is scarce concerning the followup recommendations after resection of CN or for stable CN. However, at least an abdominal US every six months should be obtained for the first few years after a CN diagnosis.[8,10,11] Our practice has been to perform US every three months for children with a history of CN.

Individuals with pathogenic germline DICER1 variation or a history of DICER1-related condition(s), including CN, renal sarcoma, PPB, or sex cord-stromal tumors, are eligible for the International PPB/DICER1 Registry. The International PPB/DICER1 Registry provides central pathology review and shares information with families and treating healthcare providers.

CN is a benign renal tumor affecting adults and children and can be associated with DICER1 mutation. In childhood, males are more affected by CN, while women are more affected in adulthood.[12] Diagnosis is usually made within the first four years of life but has been made in teenagers up to 14 years of age. Symptoms can be a sensation of an abdominal mass, abdominal pain, hematuria, or urinary tract infection. The most common imaging modality used is abdominal US, which demonstrates an intrarenal complex mass, hypo or avascular, with a capsule and multilocular cysts separated by septae. At this point, it can be challenging to make the difference between a CN and a more differentiated cyst based solely on imaging. The only way to confirm it is on the pathological specimen of resection.[8]

Thus far, the risk of DICER1-associated CN for malignant transformation appears low; however, most cases of CN have been resected. In addition to the prevention of malignant transformation, early resection may also be nephron-sparing. Unfortunately, however, children with DICER1-related CN have a risk for bilateral disease. To date, the literature suggests removing larger or symptomatic cysts with surgery. Surgery is the only management option for CN; preoperative neoadjuvant chemotherapy is not suggested.[13]

Smaller CN lesions could be followed using only US, but more complex features should raise suspicions and lead to anatomical imaging.[2] A recent case report and research by McGill University addressed the risk of transformation of CN in ASK. It seems that ASK may arise from a pre-existing CN, a continuum analogous to the type I PPB cysts becoming a type II or III PPB.[1,2,14,15] With this new information in mind, the questions of early diagnosis and removal of smaller cysts emerge.

In this case, we highlight the challenge of managing CN in the setting of genetic predisposition, which included bilateral and recurrent CN.

## Conclusions

This case highlights the dilemma between removal vs. followup of small kidney cystic masses in patients with DICER1 pathogenic variation. Here, the option of surveillance was initially adopted, but resection became necessary as the CN rapidly increased in size.

**Competing interests:** The authors report no competing personal or financial interests related to this work.

This paper has been peer-reviewed.

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