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Original contribution

# Pediatric cystic nephromas: distinctive features and frequent *DICER1* mutations☆

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**Summary** Cystic nephromas (CNs) are uncommon benign renal neoplasms that present with a bimodal age distribution, affecting either infants/young children or adult females. Although differences between these age groups have been suggested, large studies of pediatric CN have not been conducted. As a result, the nomenclature and diagnostic criteria for these lesions remain controversial. In addition, the morphological overlap seen between CN and cystic partially differentiated nephroblastoma (CPDN) can result in diagnostic dilemmas. This study reviews the morphologic and radiographic features of 44 pediatric CN prospectively enrolled on a Children's Oncology Group protocol from 2007 to 2013. Although the typical multicystic architecture with thin septa described in adult CN was present in all of our pediatric cases, differences were also identified. We report distinctive features that add to the morphological spectrum of CN in children. Of the 44 cases, 16 had been previously analyzed and reported for *DICER1* mutation, and either loss of function or missense mutations or both were identified in 15 of 16. In contrast, we analyzed 10 cases of adult CN, and all were negative for *DICER1* mutations; similarly, 6 CPDNs previously analyzed and reported were negative for *DICER1* mutations. Therefore, the clinical, morphological, and genetic differences between pediatric and adult CN, as well as between CN and CPDN, suggest that these 3 lesions represent distinct entities.


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## 1. Introduction

Cystic nephromas (CNs) are uncommon benign renal neoplasms almost exclusively reported in 2 distinct groups:

in infants/young children of both sexes and in adult females [1,2]. Originally referred to as multilocular renal cysts [2-4], CNs are characterized by an architecture that is exclusively multicystic and by the exclusive presence of mature nephrogenic elements [5]. In recent years, pediatric CNs have received more attention due to the documentation of familial cases linked to *DICER1* germ line mutations and familial pleuropulmonary blastoma (PPB) [6-8]. A *DICER1*–PPB tumor predisposition syndrome is now recognized in which the main phenotypic spectrum includes PPB, pediatric CN, ovarian Sertoli-Leydig tumors, and multinodular goiter [9,10]. A recent study has also documented the presence of *DICER1* mutations in the majority of the pediatric CNs selected for analysis [11].

Although differences between adult and childhood CN have been suggested [1], large studies detailing the morphological spectrum and radiographic appearance of pediatric CN have not been conducted. The use of the same nomenclature applied to both age groups has raised controversy [12,13]. In addition, pediatric CNs are often included within the spectrum of cystic partially differentiated nephroblastomas (CPDNs), which differ from CN only by the presence of immature nephrogenic elements. However, some authors have recommended that CN and CPDN should be treated as distinct entities [5]. The absence of *DICER1* mutations in all 6 CPDNs analyzed supports the notion that CN differs from CPDN [11]. In the current study, our goal is to review the pathologic, radiographic, and where possible the genetic features of a large cohort of pediatric CNs prospectively registered on a cooperative group protocol to delineate their morphological spectrum and to investigate a possible correlation between morphological features and *DICER1* mutation status.

## 2. Materials and methods

### 2.1. Case selection

Forty-four CNs were registered on the AREN03B2 protocol of the Children's Oncology Group from March 2007 to July 2013. A full set of slides was available for all cases, ranging from 4 to 56 slides. Available clinicopathological information included patient age, sex, tumor laterality, type of surgical procedure, and specimen diameter and weight. Contrast-enhanced abdominal imaging studies were available in 42 cases (39 computed tomography [CT], 2 magnetic resonance imaging [MRI], 1 both CT and MRI). In addition, chest CT was available for review in 39 cases. All available scans in this cohort were independently reviewed by 2 pediatric radiologists (G. K. and E. A. S.). Disagreements were resolved by a consensus review of the images.

For comparative *DICER1* mutation status, unstained slides from 10 unselected adult renal lesions classified as CN were retrieved from the Department of Pathology files at Vanderbilt University Medical Center between 2000 and 2013. All patients were female with an age at presentation ranging between 31 and 75 years old (average, 58 years).

### 2.2. *DICER1* mutation status

Of the 44 pediatric patients in this study, *DICER1* mutations had been previously been determined by sequencing in 16 patients, as previously published [11]. Nonsense and frameshift mutations were classified as "mutation–loss of function" (M-LOF), and missense variants were classified as "mutation-hotspot" (M-HS), all of which were documented to be damaging through the (Sorting Intolerant from Tolerant) algorithm (http://sift.bii.a-star.edu.sg/). The 10 adult renal lesions classified as CN were analyzed for *DICER1* mutation using the same methods.

## 3. Results

### 3.1. Clinicopathological features

The age at presentation of the 44 pediatric CNs varied from 7 days to 14 years; however, the majority presented during infancy, and only 2 presented beyond 49 months of age (at 12 and 14 years of age, both females). Excluding these 2, the median age of presentation was 16 months. Of the 44 cases, 22 were female and 22 were male; 22 involved the left kidney; and 22, the right kidney. One patient had 2 discrete masses in the left kidney. Complete nephrectomy was performed on 41 patients and partial nephrectomy on 3 patients. All 44 were stage 1 and completely excised. None recurred. The tumors ranged from 6 to 16.5 cm (median, 10.6 cm) in diameter, and the nephrectomy weight ranged from 35 to 1361 g (median, 540 g).

### 3.2. Radiographic features

Contrast-enhanced CT or MRI of the abdomen/pelvis was available in 42 cases and demonstrated 43 renal cystic lesions (1 patient had 2 cystic masses). The volume of the renal cystic mass ranged from 82.68 to 1320.06 mL (mean, 538.9 mL; median, 517.15 mL). In the axial dimension, the maximum dimension ranged from 5.0 to 13.7 cm. Based on the imaging classification system used for renal cysts in adults proposed by Bosniak [14], the distribution of the lesions was as follows: Bosniak 1, 1 (2.5%); Bosniak 2, 0 (0%); Bosniak 3, 40 (93%); Bosniak 4, 2 (4.7%). Calcification was seen in only 1 case. A pseudocapsule, defined as a thin rim of tissue demarcating the margin of the lesion from the adjacent renal parenchyma, was present in 37 (86%) of the masses by imaging; the other 6 masses did not have a pseudocapsule based on poor margination from the normal renal parenchyma (Fig. 1A and B). The cystic mass closely abutted the renal pelvis in all 42 cases and showed protrusion/herniation into the renal pelvis in 18 cases (41.9%) (Fig. 1C and D).