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Pediatric Cystic Nephromas: Distinctive Features and Frequent *DICER1* Mutations

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Abstract

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 remains 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 (COG) protocol from 2007 to 2013. While 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 15/16. In contrast, we

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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 three lesions represent distinct entities.

Keywords

cystic nephromas; *DICER1*; cystic partially differentiated nephroblastoma; pediatric renal tumors

1. Introduction

Cystic nephromas (CNs) are uncommon benign renal neoplasms almost exclusively reported in two distinct groups: in infants/young children of both genders 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 CN have received more attention due to the documentation of familial cases linked to *DICER1* germline 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 morphologic 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 six 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 in order to delineate their morphological spectrum and to investigate a possible correlation between morphological features and *DICER1* mutation status.

2. Material 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 clinicopathologic information included patient age, gender, 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 two pediatric radiologists (GK, EAS). 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 SIFT. The 10 adult renal lesions classified as CN were analyzed for *DICER-1* mutation using the same methods.

3. Results

3.1 Clinicopathologic Features

The age at presentation of the 44 pediatric CN varied from 7 days to 14 years, however the majority presented during infancy, and only two presented beyond 49 months of age (at 12 and 14 years of age, both females). Excluding these two, 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 two 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 35g to 1361g (median 540g).

3.2 Radiographic Features

Contrast enhanced CT or MRI of the abdomen/pelvis was available in 42 cases, and demonstrated 43 renal cystic lesions (one patient had two cystic masses). The volume of the renal cystic mass ranged from: 82.68-1320.06 cc (mean: 538.9 cc, median: 517.15 cc). In the axial dimension, the maximum dimension ranged from 5.0-13.7 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 (Figure 1 A-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%) (Figure 1 C-D).

Chest CT demonstrated coexisting cystic lung masses in 4 cases. These included a 9 cm multicystic mass in one child, a single 1.2 cm right lung cyst in a second child, 2 left lung cysts (1cm and 0.2cm) in a third child, and bilateral solitary cysts measuring 0.6-0.8 cm in the fourth child (Figure 1 E-F).

3.3 Histopathologic Features

All 44 cases showed an exclusively cystic appearance with multicystic architecture, simple cysts, and absence of immature nephrogenic elements, consistent with the diagnosis of CN. Sampling of pelvicaliceal structures was present in 39 cases, and in all 39 the lesion was in close proximity to these structures, either abutting them or protruding into the renal pelvis. In 18 cases, a direct contiguity between the lesion and either the renal pelvis, calices or papillae was observed (Figure 2). The epithelium lining the cysts ranged from flattened to cuboidal, with frequent hobnail features. The septa were hypocellular and showed variable degrees of collagenization and edema. In most cases, variable amounts of mixed inflammation were seen within the septa, as well as small foci of recent hemorrhage and hemosiderin-laden macrophages. No areas of ovarian-type stroma, stromal hypercellularity or cytological atypia were found. Furthermore, no definitive solid areas or areas of epithelial complexity (branching glands, papillary projections or cribriform features) were seen.

There were two features that were variable within our population of pediatric CNs: encapsulation and architectural complexity. First, in 24 cases a fibrous pseudocapsule (often containing entrapped tubules and glomeruli) surrounded the lesion entirely (54.5%), whereas in 20 cases (45.5%) the CN was poorly demarcated (Figure 3) with only partial presence (11 cases) or complete absence (9 cases) of a pseudocapsule, resulting in cysts intermingling with the normal adjacent parenchyma. Second, there were differences in the overall architectural complexity in these pediatric CN, as determined by variation in septal thickness, variation in cyst size and shape, and degree of pericystic stromal condensation (Figure 4). In 24 cases (55%) these features were either absent or focal and restricted to the transition with the normal parenchyma. However, in 20 cases (45%) these features were prominent, involved the majority of the lesion, and conferred a more complex architecture reminiscent of multicystic dysplasia. These two pathologic features were analyzed using Chi-square exact test in all 44 patients, and were found to be significantly associated with each other: patients with poorly encapsulated CN were more also more likely to have prominent architectural complexity ($p=0.0005$).

3.4 *DICER1* mutation status

Of the 44 pediatric CN included in this study, the *DICER1* mutation status had been previously published for 16 [11]. Of these, 15 contained *DICER1* mutations: 12 CN contained both *DICER1* M-LOF and M-HS mutations and 3 CN contained only M-HS mutations. Of the four patients with concurrent pulmonary cysts, 2 had *DICER1* mutation status available and both contained both M-LOF and M-HS mutations. *DICER1* mutation status was not available for the two older girls with CN. All 10 adult CNs were negative for *DICER1* mutations.

Given the morphologic heterogeneity observed, we analyzed the association between the different types of *DICER1* mutation (in the 16 cases for which this was available) and the two heterogeneous pathologic features observed (encapsulation and architectural complexity), but found no statistical correlation (p-values greater than 0.05) when comparing those tumors with *DICER1* M-LOF mutations compared with those lacking M-LOF mutations.

4. Discussion

To our knowledge, this study contains the largest series of pediatric CN described to date in the literature. While the morphological spectrum of adult CN has been extensively studied [3, 4, 15-17], limited data has been published on pediatric cases [1, 5]. The relationship between adult and pediatric CN has long been controversial. The latest World Health Organization (WHO) and International Society of Urologic Pathology (ISUP) classification schemes refer to CN as an adult neoplasm without mentioning its occurrence in pediatric patients [18-19]. Therefore, most of the existing literature and current diagnostic criteria for CN are based on adult cases, posing a challenge to the diagnostic approach of pediatric lesions. In contrast, within the pediatric pathology literature, CN is commonly considered together with CPDN, an entity that is virtually absent in adults [13]. Therefore, review of this series of 44 pediatric CN allows us to delineate their morphological and radiographic spectrum and draw some conclusions about their relationship to adult counterparts and CDPNs, including the role of *DICER1* mutation.

In addition to the older age at presentation and the female gender predilection in adult cases, morphological differences between adult and pediatric CN have been previously suggested [1]. Our results confirm these differences. Although many features described in adult CN were seen in our cases, none contained the ovarian stroma or stromal hypercellularity that is seen to variable degrees in most adult cases [1, 15, 16]. While many of our pediatric CNs were poorly encapsulated, a complete fibrous pseudocapsule is described as a constant feature in adult CN. Although the presence of architectural complexity has been described in a small subset of adult CN [15], those features are more prevalent in our series of pediatric CN (45.5% of all cases). Some features of architectural complexity have also been described as part of the spectrum of mixed epithelial and stromal tumor (MEST), an entity showing significant morphological and molecular overlap with adult CN [15-17, 19]. However, none of our cases presented additional diagnostic features of MEST that could justify this diagnosis, such as solid areas, stromal hypercellularity or complex epithelial lesions (including branching glands, papillary projections or cribriform architecture). Finally, we were not able to identify any previously reported cases of MEST occurring in the pediatric population cohort.

We observed morphologic heterogeneity among pediatric CNs that involved the degree of encapsulation and the architectural complexity. In addition, the pelvicaliceal structures (renal pelvis, calices or papillae) were often involved with direct contiguity between the lesion and these structures both pathologically and radiographically. Studies of *DICER1* gene disruption performed in animal models demonstrate aberrant development of the collecting system and renal cystic and dysplastic changes [20-22], suggesting that *DICER1* plays a role

in the development of the collecting system during normal kidney morphogenesis. Therefore, the contiguity between the lesion and pelvicaliceal structures raises the possibility of a developmental component in the pathogenesis of pediatric CN.

The previous reports of CN imaging findings have likewise included both adult and pediatric patients [1, 23, 24] and describe well-circumscribed, encapsulated, cystic mass with septations. Though a pseudocapsule was present by imaging in the vast majority of our cases, 14% lacked a pseudocapsule on imaging. In agreement with previously published literature, 93% of our cases had a Bosniak 3 appearance, while 3 lesions were classified as Bosniak 4 (2 cases) and Bosniak 1 (1 case). In our series of 42 children, the tumor closely abutted the renal pelvis in all cases, with protrusion/herniation into the renal pelvis noted in 18 cases on both imaging and pathology.

In addition to these observations, our results further emphasize the high prevalence of *DICER1* mutations in pediatric CN, as previously published in an unselected group of CN [11]. Importantly, our demonstration of the lack of *DICER1* mutations in a cohort of unselected adult CN further supports the existence of differences between adult and pediatric cases. The same is true for CPDN: the absence of *DICER1* mutations in six CPDN [11] also supports a distinction between CN and CPDN.

In summary, our findings delineate the morphological spectrum of a large series of pediatric CN, with acknowledgement of a few distinctive morphological features: contiguity with pelvicaliceal structures, lack of encapsulation, and areas of more complex architecture. The existence of clinical, morphological and genetic differences between pediatric and adult CN, and between CN and CPDN supports the hypothesis that they represent three distinct entities that should be classified independently.

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Figure 1.

Radiographic features of pediatric cystic nephromas. Well-circumscribed cystic mass with pseudocapsule as described in adult CN (A); some cases of pediatric CN lacked a pseudocapsule (B). Relationship of pediatric CN to renal pelvis: axial T2-weighted image shows the cystic mass abutting the renal pelvis without herniation (C); coronal T2-weighted image shows herniation of the cystic renal mass into the renal pelvis and proximal ureter (D). Co-existing pulmonary cysts at initial presentation of pediatric cystic nephroma: solitary pulmonary cyst in a 13 month old (E) who had bilateral lesions, and large cystic pulmonary mass in a 16 month old (F).

Figure 2.
Involvement of pelvicaliceal structures by pediatric cystic nephromas, with direct extension of the lesion from the renal papillae (A, B) and renal pelvis (C, D).

Figure 3. Fibrous pseudocapsule (A) and simple architecture with thin septa (B) as described in adult cystic nephroma. Many cases of pediatric cystic nephroma lacked encapsulation and showed a direct interface with the adjacent normal parenchyma (C, D).

Figure 4.

Areas of increased architectural complexity reminiscent of multicystic dysplasia seen in pediatric cystic nephromas, with thicker septa, greater variation in cyst size and shape with more numerous small cystic structures (A-C) and frequent pericystic stromal condensation (B, D).