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The Association between Autosomal Dominant Polycystic Kidney Disease and Renal Cell Carcinoma

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Abstract

Objectives: The relationship between autosomal dominant polycystic kidney disease (ADPKD) and renal cell carcinoma (RCC) is investigated to determine a link that would guide management due to elevated RCC risk. Current literature is inconclusive on this topic. Methods: This study is a retrospective chart review of patients having undergone nephrectomy. Those with pathology and history consistent with ADPKD were reviewed for presence of RCC. Results: The review at this institution revealed RCC in 18% of ADPKD patients who underwent nephrectomy. These rates are significantly higher than those found in the general population, and even greater than those would be expected in patients suffering end-stage renal disease (ESRD). Conclusions: Due to the increased prevalence of RCC in ADPKD, clinicians managing patients with ADPKD should maintain a high index of suspicion. Our data suggest a link between ADPKD and RCC, most likely at the genetic level. In light of this, we feel that further genetic research is needed to potentially discover the link between these two disease processes.

Keywords

Autosomal Dominant Polycystic Kidney, Chronic Kidney Failure, Genetic Variation, Nephrectomy, Renal Cell Carcinoma

1. Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal cystic disease

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affecting up to 1:400 people [1]. Approximately 5% of people in the United States with end stage renal disease requiring renal replacement therapy (RRT) can be attributed to an underlying pathology of ADPKD [2] [3]. Renal cell cancer (RCC), on the other hand, is a fairly rare disorder affecting only 10 - 20 per 100,000 [4]. The connection between these two diseases has been postulated, but currently, ADPKD is not held to be a risk factor for the development of RCC. This may be secondary to the limited number of cases, as well as confounding factors. It has been shown, however, that those with ADPKD develop RCC earlier than the general population and that many signaling proteins implicated in cancer are upregulated in individuals with ADPKD [5] [6]. Our institution reported the prevalence of RCC in nephrectomy specimens of ADPKD patients up to the year 2010 [7]. The goal of this study is to update the data and to review the current literature regarding this clinical entity.

2. Methods

After obtaining IRB approval (approval # L15-021), all nephrectomies performed in our institution from May 2010 to October 2014 were reviewed yielding 229 cases. World Health Organization criteria were used for classification of all cases [8]. Those cases with pathology and history consistent with ADPKD were included while those with renal cystic disease from all other causes were excluded. A total of 16 cases met the qualifications for ADPKD [9]. Pathology for these cases was reviewed for the presence of RCC.

Pubmed was systematically reviewed using “renal cell carcinoma” and “autosomal polycystic kidney disease” as keywords and subsequent survey for case reports and case series, yielding 42 papers published within the last 10 years regarding the incidence of RCC in ADPKD patients (see **Table 3** summarizing these papers). The vast majority of these papers state that there is no generally accepted association between ADPKD and RCC, but most do not refute the possibility due to lack of statistically significant numbers of patients in trials.

3. Results

16 cases of ADPKD were identified between May 2010 and October 2014 (**Table 1**). Of these cases there were 2 out of 16 pathology reports that revealed the presence of RCC (13%). The median age was 54 years. Of the 2 patients identified with RCC, one had a 10-year history of RRR, while the other had a 1-year history of RRT. The RCC subtypes identified were clear cell and mixed (clear cell, papillary, sarcomatoid).

In a prior ADPKD study from our institution by Lane *et al.*, 2 cases of RCC were found out of 6 cases of nephrectomy (**Table 2**) [7]. Combining their data with the current study gives a total of 4 cases of RCC among 22 nephrectomies (18%) from 2007 until 2014 at our institution.

Figure 1 illustrates a representative histological example of an ADPKD kidney specimen showing features of cysts and dysplastic ducts (**Figure 1(a)**), as well as harboring an area of renal cell carcinoma within the parenchyma of the same kidney (**Figure 1(b)**).

4. Discussion

A possible association between RCC and ADPKD was first suspected and described by Walters and Brasch in 1934 [10]. Their findings were initially considered to be coincidental, but over 60 case reports and case series have supported their hypothesis [6] [11]-[13]. The results from our institution’s case series endorse the same ideation. Despite this, some clinicians have continued to dispute any association between these two disease processes. Even in the recent literature, there is still no consensus regarding ADPKD and the associated risk for RCC [6] [11] [14]-[17].

When considering autopsies of deceased ADPKD patients, RCC is not listed under the most common causes of mortality [17]. Therefore, many clinicians believe that the issue of RCC in ADPKD patients is not relevant. In addition, the presence of RCC in the specimen is easily missed. The RCC tumor clusters can be small and easily “overlooked”, particularly if the pathologist is not suspicious of these lesions [6] [18]. In contrast to sporadic RCC, the diagnosis of RCC in ADPKD kidneys can only be made in surgical specimens. Imaging studies fail to confirm or rule out RCC, making this a more difficult diagnosis in these patients. Thus, the true prevalence and incidence in ADPKD patients cannot be determined. This may explain why some studies do not demonstrate any significant statistical support for the association of ADPKD and RCC.

Regardless which side of the discussion is favored, nearly all agree that the sample size is too small. There simply are not enough cases to statistically support either argument [6] [11] [18] [19]. This case series is intended

Table 1. Summary of clinical data and histopathological features of the patients who underwent unilateral or bilateral nephrectomy due to ADPKD from the years 2010 until 2014.

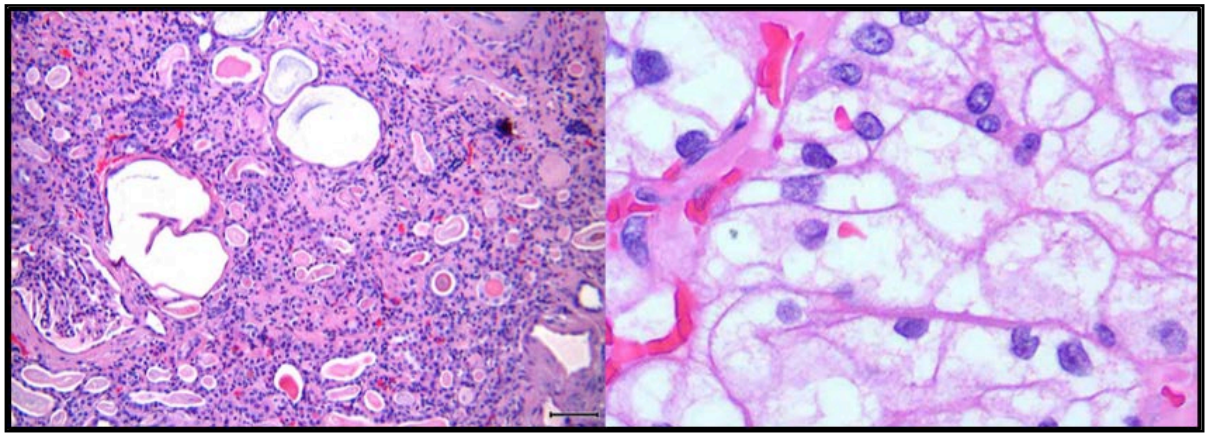
Age	Sex M/F	Ethnicity Hispanic = 0, White = 1 Black = 2, Other = 3	Year of Nephrectomy	Indication for nephrectomy Size = 1, Calcifications = 2 Solid mass = 3, Other = 4	Time on RRT† prior to nephrectomy (years)	RCC‡ No = 0 Yes = 1	RCC‡ features	Tumor Size (cm) L/R
59	M	1	7/2010	2	0	0		
57	F	3	7/2010	2	5	0		
53	F	1	8/2010	4	0	0		
68	M	1	2/2011	2	4.5	0		
58	F	1	2/2011	3,4-retroperitoneal bleed	10	1	Mixed (clear cell, papillary, sarcomatoid)	(6) L
61	M	1	5/2011	2	0	0		
57	M	1	5/2012	4-infections	0	1	Papillary Adenoma	(0.4) L
58	F	1	6/2012	3	0	0		
57	M	0	6/2013	4-recurrent hematoma	7	0		
57	M	1	7/2013	1	2.5	0		
58	F	1	12/2013	1	0	1	Papillary Adenoma	(0.3) L
67	F	3	1/2014	1, 2, 3	0	0		
43	F	0	2/2014	1	6	0		
45	M	1	5/2014	1	1	0		
44	M	1	8/2014	1	1	1	Clear Cell	(5) R
52	M	1	8/2014	1	0.25	0		

†Renal Replacement Therapy, ‡Renal Cell Carcinoma.

Table 2. Lists a previous series of ADPKD patients undergoing nephrectomy at our institution in the years 2007 through 2010. Three out of six patients had confirmed RCC. These data were published in 2011 [7].

Age	Sex M/F	Year of Nephrectomy	Indication for nephrectomy Size = 1, Calcifications = 2 Solid mass = 3, Other = 4	Time on RRT† prior to nephrectomy (years)	RCC‡ No = 0 Yes = 1	RCC‡ features	Tumor Size (cm) L/R
64	F	6/2010	1	2.5	1	Papillary Adenoma	(0.4) L/(0.4)R
59	M	5/2010	2	0	0	-	-
57	M	5/2009	3	3	1	Clear Cell	(1.1, 0.55) L/(0.2) R
41	F	11/2008	1	2	0	-	-
50	F	6/2007	1	1.5	0	-	-
51	M	5/2007	1	*	1	Clear Cell	(3.5) R

†Renal Replacement Therapy, ‡Renal Cell Carcinoma, *Data Not Available.



(a) (b)

Figure 1. (a) A representative example of a polycystic kidney composed of cysts in different sizes (hematoxylin and eosin staining; ×100); (b) Renal cell carcinoma with pleomorphic nuclei removed from a tumor nodule in the same kidney specimen as shown in **Figure 1(a)** (hematoxylin and eosin staining; ×400).

to expand the pool of data, so that sufficient numbers will be available to complete epidemiologic studies on this phenomenon in the future.

According to the National Cancer Institute SEER program, the incidence of sporadic RCC is estimated to be 21.02 per 100,000 in men and 10.4 per 100,000 in women [4]. Amongst these cases the most common variant of RCC is clear cell carcinoma, accounting for nearly 80%. This is followed by papillary carcinoma, which contributes 15% of the RCC variants [20] [21].

Irrespective of the variant diagnosed via specimen histology, all subtypes initially originate within the renal cortex and have common, well-established risk factors. Smoking, hypertension and obesity are considered weak risk factors for RCC; however, ESRD is unequivocally considered a major risk factor for this malignancy. Bonsib *et al*. reported rates as high as 8% of RCC in patients with ESRD or undergoing dialysis for an average of 9 years [17].

The association of RCC and ESRD is widely accepted in the literature [6] [11] [17] [18]. The prevalence of RCC in ESRD patients is significantly higher than the prevalence of sporadic RCC in the general population (by a factor of 1000), and therefore, ESRD is a well-established risk factor for this malignancy. Because the majority of ADPKD patients develop ESRD requiring long-term dialysis, some clinicians assume that their ESRD status alone is the only significant and relevant risk factor for RCC. On the contrary, numerous studies have demonstrated that the rates of RCC in ADPKD patients are still higher when adjusted for time spent on dialysis and compared with ESRD patients whose kidneys failed due to other causes than ADPKD [6] [18].

When compared to RCC, ADPKD is much more common in the general population. Genetic mutations associated with the disease are as common as 1 per 1000, or at least one hundred times more prevalent than RCC. There are three common mutations currently known and related to ADPKD pathogenesis: PKD1, PKD2, and PKD3. Chromosome 16 houses the mutation in PKD1, which accounts for 85% of APKD cases. PKD2, found on chromosome 4, is much less common [1]. According to current literature, the significance of determining the specific mutation helps stratify the risks and prognosis of disease progression. PKD1 mutations are associated with much earlier onset of ESRD than PKD2 [22].

While there is a much higher incidence of ESRD development in ADPKD patients, and ESRD leads to higher RCC risk, the data obtained at our institution supports the hypothesis that ADPKD patients still demonstrate higher rates of RCC than would be expected by ESRD alone. Furthermore, RCC in ADPKD patients develops at much younger ages (average 47 years) and is often bilateral (29%) and multicentric (25%) [12]. These rates are significantly higher than those found in sporadic RCC development, with 61 years being their median onset, 2% - 6% are bilateral, and only 5% are multicentric [12] [13] [22]. These clinical features of RCC in the ADPKD population are specific and unique, and the increased prevalence could be attributed to the associated ADPKD genetics and pathophysiology.

The data collected at our institution and presented in this papersupport this relationship with an 18% preva-

lence of RCC in ADPKD patients. Hajj and other clinicians described rates varying from 5% to 12% depending on the time frame of RRT. Although these rates are high, some researchers argue that they are low estimates. Soft tissue nodules, which may harbor RCC within the ADPKD specimen after nephrectomy, can easily be overlooked, in particular, when the clinician does not alert the pathologist that RCC is suspected. One purpose of this paper is to make clinicians and pathologists more attentive to this issue when submitting kidney specimens of ADPKD patients.

By restricting our epidemiologic pool to patients with nephrectomy, many proponents believe that the prevalence of RCC in ADPKD is underreported [6] [18]. Comparing these rates to the previously mentioned 0.021% prevalence of sporadic RCC in the population or the 4.8% prevalence of RCC in ESRD patients further supports the hypothesis of strong association between ADPKD and RCC.

With the literature equivocal regarding an increased risk for RCC in ADPKD, there is a lack of clear guidance regarding early nephrectomy in patients who develop new or growing soft tissue nodules within their kidneys. **Table 3** provides an overview of the body of literature published on the topic "RCC in ADPKD" [11] [12] [18] [23]-[30]. A review of these studies shows that the majority of investigators and clinicians acknowledge a link between ADPKD and the risk for RCC beyond the current risk associated with ESRD.

Table 3. Literature review.

Age	Sex	Involvement L/R	RCC[‡] pathology	RRT[†] (years)	Citation
58	M	Bilateral	Papillary Renal Cell Carcinoma	0	[11]
32	M	Bilateral	Papillary Renal Cell Carcinoma	0	[11]
45	M	R	Clear Cell and Papillary Renal Cell Carcinoma (17 foci)	10	[12]
*	M	L	Papillary Non-Invasive Urothelial Carcinoma	0	[18]
*	M	L	Multi-locular Cystic Renal Cell Carcinoma	5	[18]
*	M	Bilateral	Papillary Renal Cell Carcinoma	0	[18]
*	M	R	Papillary Renal Cell Carcinoma (2 foci)	2.5	[18]
*	M	L	Clear Cell Renal Cell Carcinoma	1	[18]
*	M	L	Papillary Renal Cell Carcinoma	3	[18]
*	M	R	Clear Cell and Papillary Renal Cell Carcinoma	3	[18]
*	M	L	Papillary Renal Cell Carcinoma	5	[18]
*	M	R	Papillary Renal Cell Carcinoma (2 foci)	2.5	[18]
*	M	R	Clear Cell Renal Cell Carcinoma	0	[18]
*	F	R	Clear Cell Renal Cell Carcinoma (1 focus), Papillary Adenoma (<0.5 cm, current guidelines classified as adenoma)	7	[18]
*	F	L	Papillary Adenoma (<0.5 cm, current guidelines classified as adenoma)	0	[18]
*	M	R	Cysts with Polypous and Papillary Proliferation	0	[18]
*	M	R	Cysts with Polypous and Papillary Proliferation	4	[18]
*	F	R	Cysts with Polypous and Papillary Proliferation	0	[18]
*	M	L	Papillary Renal Cell Carcinoma	0	[18]
67	F	L	Clear Cell Renal Cell Carcinoma	11	[23]
57	M	L	Papillary Renal Cell Carcinoma	7	[24]
47	M	R	Clear Cell Renal Cell Carcinoma	*	[25]
58	F	R	Clear Cell Renal Cell Carcinoma	0	[26]
57	M	L	Clear Cell Renal Cell Carcinoma	10	[27]
58	M	Bilateral	Papillary Renal Cell Carcinoma	19	[28]
68	F	L	Clear Cell Renal Cell Carcinoma	8	[29]
47	M	Bilateral	Renal Cell Carcinoma (unspecified)	0	[30]

[†]Renal Replacement Therapy, [‡]Renal Cell Carcinoma, [*]Data Not Available.

According to our data, approximately 18% of these ADPKD cases harbor RCC within their kidneys. Therefore, early nephrectomy should be seriously considered, and when possible, bilaterally in patients with nonfunctioning native kidneys. These statistics again suggest a genetic link between ADPKD and RCC. This presents a new and exciting challenge to explore the genetics of these two diseases more closely.

The main limitations of our study are related to the current diagnostic shortcomings and limited statistical data. By relying upon histopathology reports on surgical specimens, the observed prevalence is grossly underestimated and does not represent the true prevalence in all ADPKD patients. Until a less-invasive modality can prove as accurate and even timelier, the field will continue to depend on the data of surgical candidates in ADPKD. As with all rare diseases, time will provide additional data. The continual publishing of case reports and series on this topic will expand the foundation of medical knowledge and we encourage others to continue to do so. It is our hope that then physicians will be equipped with the tools and knowledge base to accurately and effectively manage RCC in ADPKD patients.

Conflict of Interest

None of the contributing authors have any conflict of interest, including specific financial interests or relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

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