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Commentary Open Access

Adult Dominant Polycystic Kidney Disease (ADPKD)

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Abstract

Autosomal-dominant polycystic kidney disease (ADPKD) is the most common inherited renal cystic disease affecting up to 10% of patients requiring some form of renal replacement therapy such as hemodialysis or kidney transplant. An association between autosomal-dominant polycystic kidney disease (ADPKD) and renal cell carcinoma (RCC) has been suspected since the 1930s. Many cases of RCC in ADPKD patients have been observed and published in the meantime. The gene mutations responsible for ADPKD have been discovered in the 1990s, however a direct genetic link to RCC has not been discovered so far, and the debate about an association between these two diseases is still controversial and ongoing. Many clinical experts who have published about this issue suspect a genetic link and state that ADPKD patients are much more prone to develop RCC than patients with end-stage renal disease (ESRD) of other causes. Currently there are no clear clinical guidelines regarding early nephrectomy in ADPKD patients with growing soft tissue nodules within their native kidneys. This commentary/review on this important clinical issue describes the experience with these patients in one institution and gives an overview of the literature.

Keywords: Adult dominant polycystic kidney disease; Renal cell carcinoma

Commentary

Autosomal-dominant polycystic kidney disease (ADPKD) is the most common inherited renal cystic disease affecting up to 1 in 400 adults [1]. This inherited kidney disease is responsible for up to 10% of patients with end-stage renal disease (ESRD), and therefore, is a major burden on public health [2]. The native kidneys are characterized by relentless development and growth of cysts in various sizes causing progressive kidney enlargement associated with hypertension, abdominal tension, gastro-intestinal symptoms, pain, and episodes of renal hemorrhage, gross hematuria, and cyst infections often severely affecting quality of life. Despite continuous destruction of renal parenchyma by progressive cystic lesions, many patients maintain adequate renal function for decades before renal replacement therapy (RRT) such as hemodialysis or kidney transplant is necessary, in many patients after the fourth decade of life. ADPKD is a systemic disorder which also can affect other organs with risks of serious complications such as massive hepatomegaly and rupture of intracranial aneurysm [3].

Polycystic changes in the kidneys have been known for over 200 years and this disease was considered as rare and incurable. With medical advances in imaging ADPKD is now diagnosed more frequently. Over the recent decades therapeutic options have evolved which have improved quality of life and lifespan significantly. These include early detection and treatment of hypertension as well as secondary comorbidities such as renal and extra-renal complications, management of chronic kidney disease-related complications, and renal replacement therapy (RRT). Gene mutations associated with this disease were discovered about 20 years ago, first the PKD1 in 1994 and then the PKD2 in 1996 accelerating basic research and a better understanding of this disease process [4,5]. Molecular genetic diagnosis for patients and family members is now available, a great asset in genetic counselling. Genetic mutations associated with ADPKD are as common as one per 1000, which means at least 100 times more prevalent than the incidence of renal cell carcinoma [6,7].

Screening of children at risk for ADPKD is currently not recommended. First-degree relatives of individuals diagnosed with ADPKD are considered at high risk. Bilateral renal ultrasound is inexpensive, widely available and is therefore the most commonly performed screening technique in adults. In the general population adults with simple cysts are more frequently seen with increasing age. Conventional ultrasound is considered as suboptimal for disease exclusion in family members of ADPKD patients, in particular when younger than 40 years and considered for living kidney donation. The finding of fewer than five renal cysts by computerized tomography (CT) scan or magnetic resonance imaging (MRI) is considered to be sufficient for disease exclusion in adults [8].

Intra-parenchymal haemorrhage and gross haematuria are frequent complications of ADPKD. Gross haematuria may occur secondary to cyst haemorrhage, nephrolithiasis, infection, and in some cases due to a malignancy (mainly from renal cell carcinoma). Bleeding into cystic lesions is often associated with fever, and clinical differentiation from cyst infection is sometimes difficult. Renal haemorrhage or gross haematuria may become more severe requiring hospitalization, but these episodes are usually self-limited and resolve within seven to ten days. Should symptoms persist, then a neoplasm should be suspected. If the patient is on blood thinners such as aspirin due to existing comorbidities, temporary discontinuation is indicated, and many clinicians recommend supportive measures such as diuretics.

The presence of fever, flank and abdominal pain, as well as of high sedimentation rate or C-reactive protein level should suspect a cyst infection; in some cases the differential diagnosis is difficult because

blood and urine cultures are often completely negative. Lipid-permeable antibiotics such as fluoroquinolones and trimethoprim-sulfamethoxazole are preferred, and in such cases percutaneous or surgical draining is indicated if patient does not improve under conservative treatment. ADPKD patients with a history of infected cysts are prone to recurrent episodes despite adequate initial antibiotic treatment. This clinical phenomenon may be explained by colonized cystic lesions or poorly perfused tissue within the kidneys.

Assigned Patient Number	Age	Sex M/F	Year of Nephrectomy	Indication for nephrectomy Kidney size=1, Renal calcifications=2, Solid mass=3, Other=4	Time on Hemodialysis prior to nephrectomy (Years)	RCC No=0, Yes=1	RCC pathology	Carcinoma diameter (cm)
1	51	M	5/2007	1	Unavailable	1	Unilateral clear cell	3.5
2	50	F	6/2007	1	1.5		-	-
3	41	F	11/2008	1	2		-	-
4	57	M	5/2009	3	3	1	Bilateral clear cell	0.2
5	59	M	5/2010	2	0		-	-
6	59	M	5/2010	2	0	0		
7	65	F	6/2010	1	2.5	0		
8	64	F	6/2010	1	2.5	1	Bilateral papillary adenomas	0.4
9	59	M	7/2010	2	0	0		
10	57	F	7/2010	2	5	0		
11	53	F	8/2010	4-severe ESRD	0	0		
12	68	M	2/2011	2	4.5	0		
13	58	F	2/2011	3, 4-retroperitoneal bleed	10	1	Mixed (clear cell, papillary, sarcomatoid)	6
14	61	M	5/2011	2	0	0		
15	57	M	5/2012	4-infections	0	1	Papillary carcinoma	0.4
16	58	F	6/2012	3	0	0		
17	57	M	6/2013	4-recurrent hematoma	7	0		
18	57	M	7/2013	1	2.5	0		
19	58	F	12/2013	1	0	1	Papillary adenoma	0.3
20	67	F	1/2014	1, 2, 3	0	0		
21	43	F	2/2014	1	6	0		
22	45	M	5/2014	1	1	0		
23	44	M	8/2014	1	1	1	Clear cell	5
24	52	M	8/2014	1	0.25	0		

Table 1: Summary of clinical data and histopathological features of ADPKD patients who underwent unilateral and bilateral nephrectomy at Texas Tech University in the years from 2007 until 2014.

A possible association between RCC and ADPKD was first suspected and published by Walters and Braasch in 1934 [9], and after more than 80 years the debate is still controversial and ongoing. First the findings were considered coincidental, but many case reports and case series have continued to support this hypothesis [7]. Some studies showed an incidence for RCC of up to 15% in surgically removed ADPKD kidneys, the majority of these tumours measuring less than 2 cm in size [7,10,11]. Table 1 lists ADPKD patients who underwent

nephrectomy and were diagnosed with RCC at our institution in the years from 2007 till 2014. Table 2 is a selection of ADPKD patients reported in the literature who were also diagnosed with RCC.

Age	Sex	Involvement L/R	†RCC pathology	‡RRT (Years)	Citation
58	M	Bilateral	Papillary Renal Cell Carcinoma	0	[15]
32	M	Bilateral	Papillary Renal Cell Carcinoma	0	[15]
45	M	R	Clear Cell and Papillary Renal Cell Carcinoma (17 foci)	10	[13]
*	M	L	Papillary Non-Invasive Urothelial Carcinoma	0	[10]
*	M	L	Multi-locular Cystic Renal Cell Carcinoma	5	[10]
*	M	Bilateral	Papillary Renal Cell Carcinoma	0	[10]
*	M	R	Papillary Renal Cell Carcinoma (2 foci)	2.5	[10]
*	M	L	Clear Cell Renal Cell Carcinoma	1	[10]
*	M	L	Papillary Renal Cell Carcinoma	3	[18]
*	M	R	Clear Cell and Papillary Renal Cell Carcinoma	3	[10]
*	M	L	Papillary Renal Cell Carcinoma	5	[10]
*	M	R	Papillary Renal Cell Carcinoma (2 foci)	2.5	[16]
*	M	R	Clear Cell Renal Cell Carcinoma	0	[10]
*	F	R	Clear Cell Renal Cell Carcinoma (1 focus), Papillary Adenoma (<0.5 cm, current	7	[10]
			guidelines classified as adenoma)		
*	F	L	Papillary Adenoma (<0.5 cm, current guidelines classified as adenoma)	0	[10]
*	M	R	Cysts with Polypous and Papillary Proliferation	0	[10]
*	M	R	Cysts with Polypous and Papillary Proliferation	4	[10]
*	F	R	Cysts with Polypous and Papillary Proliferation	0	[10]
*	M	L	Papillary Renal Cell Carcinoma	0	[10]
67	F	L	Clear Cell Renal Cell Carcinoma	11	[17]
57	M	L	Papillary Renal Cell Carcinoma	7	[18]
47	M	R	Clear Cell Renal Cell Carcinoma	*	[19]
58	F	R	Clear Cell Renal Cell Carcinoma	0	[20]
57	M	L	Clear Cell Renal Cell Carcinoma	10	[21]
58	M	Bilateral	Papillary Renal Cell Carcinoma	19	[22]
68	F	L	Clear Cell Renal Cell Carcinoma	8	[23]
47	M	Bilateral	Renal Cell Carcinoma (unspecified)	0	[24]
* Data not available † Renal Cell Carcinoma, ‡, Renal Replacement Therapy					

Table 2: Literature Review, list of published ADPKD cases diagnosed with renal cell carcinoma (RCC).

Some experts state that the true prevalence and incidence of RCC in ADPKD patients is underestimated and cannot really be determined because the diagnosis of RCC is easily "missed" in imaging studies or pathological specimens. The RCC tumour clusters are often small and easily "overlooked", in particular when the clinician does not alert the pathologist that RCC is suspected. In contrast to sporadic RCC where the diagnosis is easily made with computerized tomography (CT scan) by comparing the images before and after IV contrast administering, all currently known imaging techniques fail in the pre-surgical diagnostics of RCC in ADPKD patients. The diagnosis can only be made on pathological specimens after kidney removal. However, only few ADPKD patients undergo unilateral or bilateral nephrectomy, thus

the true prevalence and incidence of RCC cannot be determined. This may explain why some studies have not demonstrated any significant statistical support for the association of ADPKD and RCC. However, the majority of papers published on this topic still continue to support the hypothesis of an association [7,12,13].

Over many years the possible increased risk of RCC has been the most relevant clinical issue for nephrologists and transplant surgeons when treating ADPKD patients. In comparison to ADPKD, ESRD and its associated acquired renal cystic disease are well-established risk factors for RCC and have widely been accepted in the literature [11,14,15]. The prevalence of RCC in ESRD patients is significantly higher than the prevalence of sporadic RCC in the general population (by an estimated factor of 1000) [7]. Because the majority of ADPKD patients develop ESRD requiring long-term RRT, some clinicians assume that their ESRD status alone is the only relevant risk factor for RCC. However, numerous studies have demonstrated that the rates of RCC in ADPKD patients are still higher when adjusted for time spent on RRT and compared with ESRD patients whose kidneys failed due to other causes than ADPKD [10,11,14]. Furthermore, RCC develops in ADPKD patients at much younger ages (average 47 years) and is often bilateral (30%) and multi-centric (25%) [7,13], much higher than found in sporadic RCC with 61 years being their median onset, 2%-6% are bilateral, and only 5% are multi-centric [12,13]. 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.

Because the literature is equivocal regarding an increased risk of 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 native kidneys. According to our reported data, 18% of ADPKD cases harbour RCC within their kidneys [7]. Therefore, we consider early nephrectomy, and when possible bilaterally in ADPKD patients with non-functioning native kidneys. We suspect a genetic link between ADPKD and RCC. It will be an exciting challenge in the near future to search more closely for possible genetic link between these two disease entities. Confirmed genetic association between ADPKD and RCC would have significant therapeutic and prognostic implications for our patients.

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