

BILATERAL PAPILLARY RENAL CELL CARCINOMA AND ANGIOMYOLIPOMA IN PATIENTS WITH AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE: REPORT OF TWO CASES AND LITERATURE REVIEW

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We herein report two rare cases of bilateral renal neoplasms associated with autosomal dominant polycystic kidney disease (ADPKD). Case 1: Bilateral nephrectomy was performed on bilateral renal masses in a 58-year-old man with ADPKD. Case 2: Bilateral nephrectomy was performed on bilateral renal masses in a 32-year-old man with clinically suspected ADPKD. In case 1, angiomyolipoma (AML) and papillary renal cell carcinoma (PRCC) (type 1) were detected in the bilateral kidneys. In case 2, PRCC (type 1) was detected in the bilateral kidneys.

Key words: autosomal dominant polycystic kidney disease, papillary renal cell carcinoma, angiomyolipoma.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is a relatively common hereditary renal cystic disease with an incidence of approximately 1 : 1,000, mainly caused by mutations of the PKD1 or PKD2 gene. To the best of our knowledge, less than 60 cases of renal cell carcinoma (RCC) have been reported in patients with ADPKD [1-6]. Renal angiomyolipoma (AML) accounts for 2.0% to 6.4% of all renal neoplasms but no cases have been reported in the bilateral kidneys with ADPKD. In this study, we report two cases of bilateral renal tumors in ADPKD – one with bilateral RCC, the other with RCC and renal AML – and we review the literature.

Material and methods

Case 1

A 58-year-old man with familial history of ADPKD turned out to have bilateral kidney tumors following computed tomography (CT) examination. These bilateral

masses were clinically considered as RCC or renal AML in conjuncture with the findings of ultrasonography (US) and magnetic resonance imaging (MRI). One year later, a needle biopsy of the left renal tumor was performed. The mass was histologically diagnosed as RCC and left nephrectomy was subsequently performed. Two years later, right nephrectomy was performed and the patient has been under dialysis since the operation.

Case 2

A 32-year-old man was clinically suspected to have ADPKD. Both CT and US detected growing renal masses in his bilateral kidneys. Bilateral nephrectomy was subsequently performed followed by hemodialysis. The patient had no clinical findings suggestive of tuberous sclerosis complex (TSC).

Results

Macroscopically, in both cases, bilateral kidneys were enlarged and numerous cysts of various diameters re-

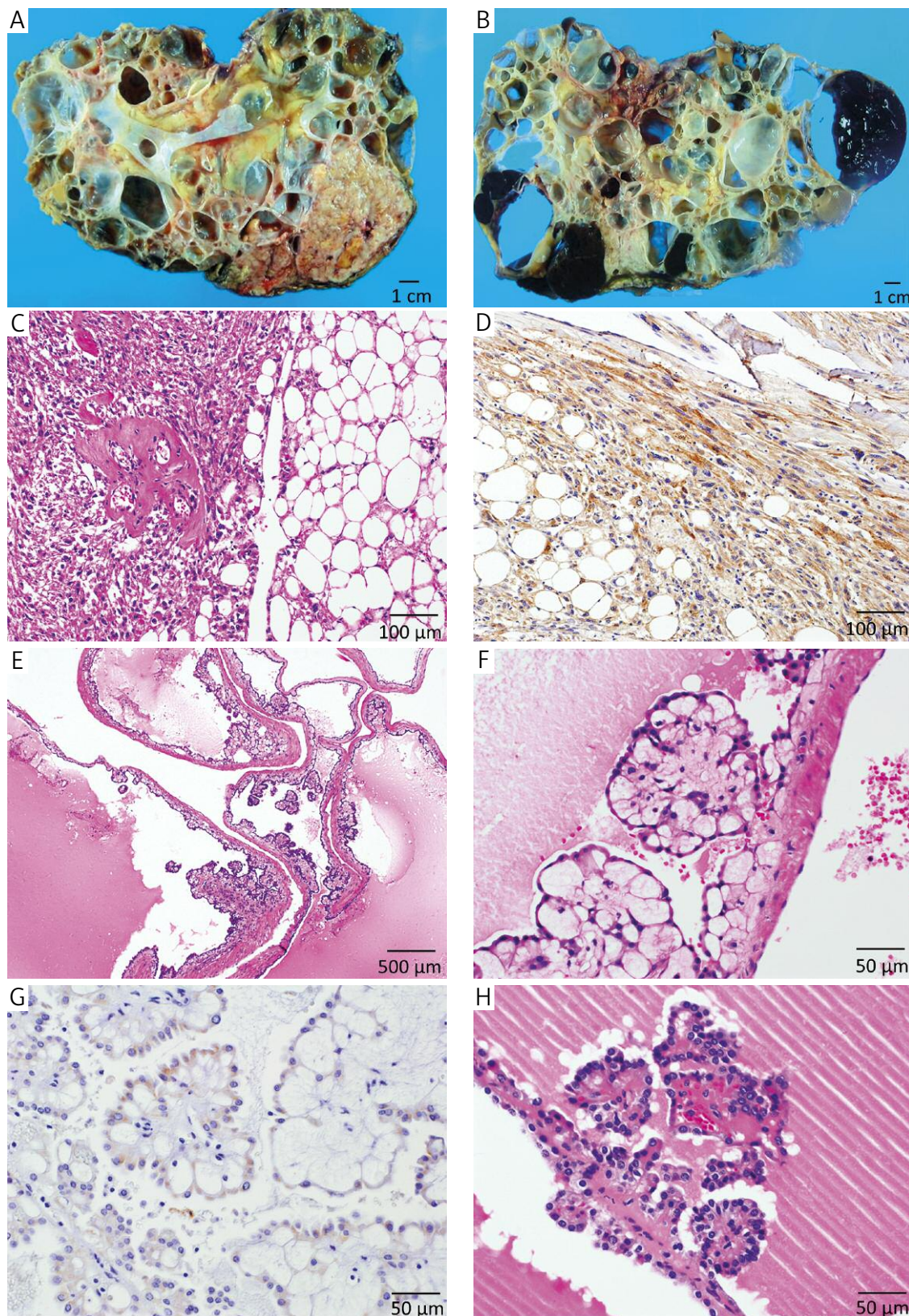


Fig. 1. In case 1, macroscopically, resected kidneys displayed masses with cysts; masses were 7 cm in the left kidney (A) and 4 cm in the right kidney (B). Microscopically, the left renal mass was angiomyolipoma (AML) composed of smooth muscle-like cells, vessels and adipocytes (C: magnification 100 \times). These cells showed positive immunoreactivity to Melan A (D: magnification 100 \times). Papillary renal cell carcinoma (PRCC) (type 1) was surrounding AML (E: magnification 40 \times , F: magnification 200 \times), and it showed positive immunoreactivity for p504s (AMACR) (H: magnification 200 \times). PRCC was observed in the right kidney as well (H: magnification 200 \times)

placed the whole renal parenchyma, consistent with ADPKD. In case 1, two masses measuring 7 cm and 4 cm in the greatest dimension were detected in the left and right kidneys, respectively (Fig. 1A, B). Microscopically, they were diagnosed as AML, composed of smooth muscle-like spindle cells, hyalinized thick-walled vessels and adipocytes (Fig. 1C). These cells were immunohistochemically positive for melanocytic and myoid markers, i.e. HMB-45, Melan A and α -SMA (Fig. 1D). In the vicinity of the AML, papillary RCC (PRCC) (type 1) was detected, characterized by a single layer of cuboidal cells (Fig. 1E, F, H). These cells were immunohistochemically positive for EMA, CD10 and p504s (AMACR) (Fig. 1G), and negative for CK34 β E12. The Ki67 labeling index of both cases was less than 1%. These findings were all consistent with PRCC (type 1). In case 2, two masses measuring 1 cm were detected in the bilateral kidneys (Fig. 2A, B). Microscopically, these tumors were also diagnosed as PRCC (type 1) (Fig. 2C-F). These cells were positive for EMA, CD10 and p504s (AMACR) (Fig. 2G, H) and negative for CK34 β E12. The Ki67 labeling index of these lesions above was also less than 1%. These findings were also consistent with PRCC (type 1).

Papillary RCC in both cases did not show any lymphatic/vascular invasion, necrosis or extrarenal invasion. TNM stages of both PRCCs were pT1, cN0, cM0, stage I.

Discussion

The association between ADPKD and RCC has remained in dispute. The state of end-stage kidney disease (ESRD) is considered to increase the overall risk of RCC developing in the patient with ADPKD: approximately half of reported cases are in the state of end-stage kidney on hemodialysis [1-8]. However, neither of the two cases in our present study were associated

with renal failure. ADPKD-associated RCC occurs in younger age groups than sporadic RCC; the median age is 45 years old with the range 29 to 67 years old [1]. The mean tumor size is 18 mm ranging from 8 mm to 50 mm [2]. The two cases were consistent with previous reports regarding their age and tumor size. The bilaterality (25%) and multifocality (29%) of RCC are also frequently reported in these tumors as in our present cases [3]. Histopathologically, Hajj *et al.* reported that clear cell RCC was the most common histological subtype in ADPKD (42%), while the incidence of PRCC was higher in ADPKD than in sporadic RCC [2]. Of 44 patients, they also reported that 9 cases (20%) were PRCC as in our present cases, significantly higher than that of the general population (12%) (Table I). Among these cases, five were type 1 and three were type 2 [3-5]. However, it is also true that ESRD developed into multiple RCC much more often compared to sporadic RCC: 1.6% to 8.0% of the patients with ESRD, of whom 23% to 58% of the patients had acquired cystic disease of kidney (ACDK) [7]. Most of the RCCs arising in ACDK are associated with specific histological features including acquired cystic disease-associated RCC (ACD-RCC) and clear cell papillary RCC [8]. However, the proportion of subtypes of RCC arising in ESRD reported by Tickoo *et al.* corresponds to that of ADPKD; papillary RCCs were relatively common (21%), while clear cell RCCs were common (43%) [8]. In addition, papillary epithelial hyperplasia and adenoma are frequently detected in ADPKD even in those without renal insufficiency and in ESRD/ACDK [1, 2, 9]. They are considered as neoplastic lesions with clinical malignant potential [9].

Genetic alterations in ADPKD-associated RCC have remained unknown. Hereditary PRCC syndrome is associated with germ line mutations of the MET oncogene located on 7q31. Sporadic PRCC typically shows

Table I. Summary of cases with papillary renal cell carcinoma (PRCC) arising in autosomal dominant polycystic disease [1-10]

CASE	AGE (YEARS)/SEX	NO. (PRCC/TOTAL)	HISTOLOGICAL TYPE OF PRCC	AD (YEARS)	REPORT
1	NA	NA	unknown	NA	Sulser, 1993 [5]
2	NA	NA	unknown	NA	Gatalica, 1994 [4]
3	58/M	2/4	unknown	16	Chang, 2007 [3]
4	69/M	NA	type 1	2	Hajj, 2009 [2]
5	45/M	2/17	type 1 type 2	10	Hajj, 2009 [2]
6	48/M	1	type 1	1	Hajj, 2009 [2]
7	64/M	2/2	type 2 type 2	0	Hajj, 2009 [2]
8	58/M	2/2	type 1	0	present case (case 1)
9	32/M	2/2	type 1	0	present case (case 2)

No. – number of tumors, AD – artificial dialysis, NA – not available

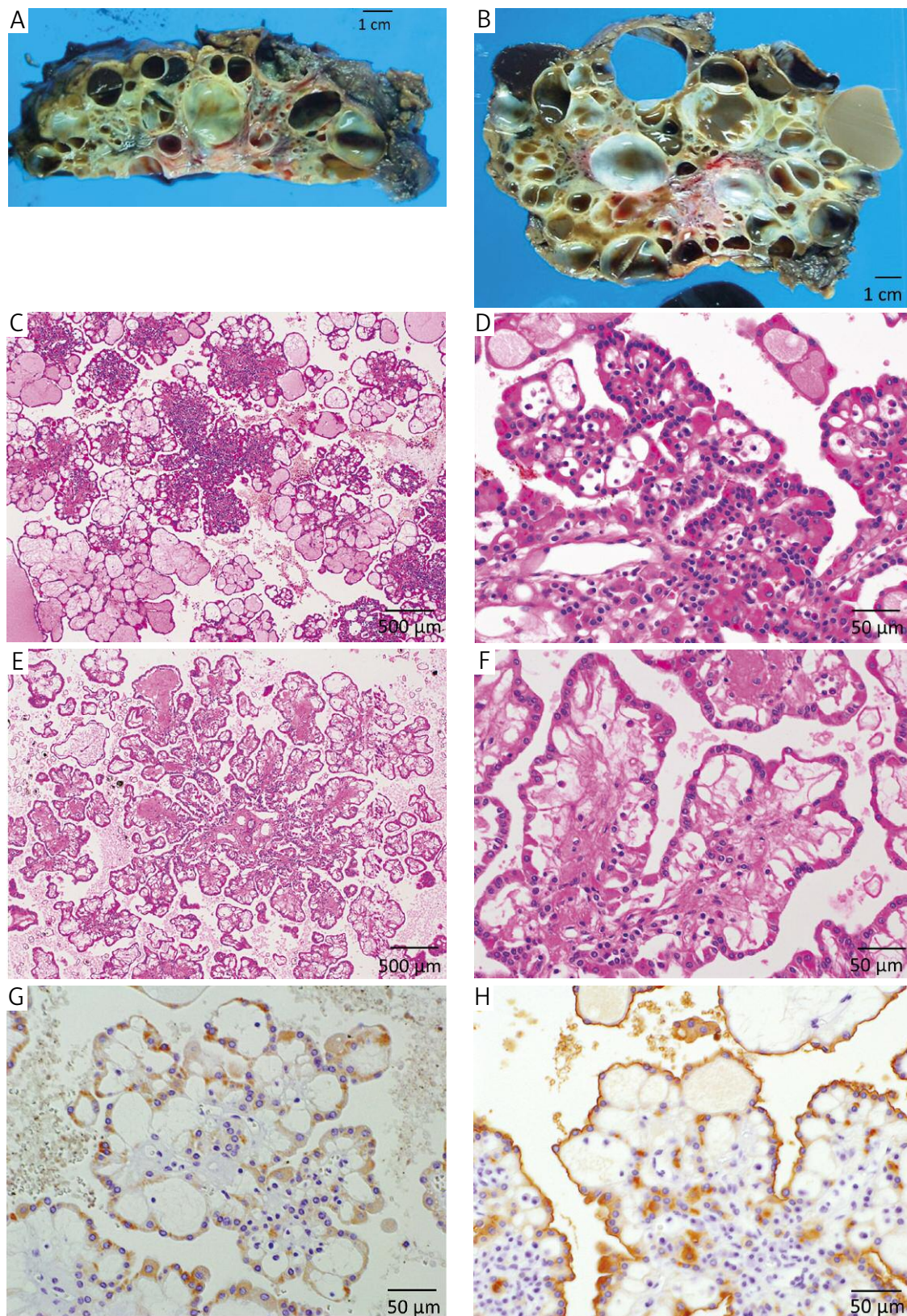


Fig. 2. In case 2, macroscopically, the left kidney (A) and the right kidney (B) displayed masses measuring 1 cm with cysts. Microscopically, the mass of the left kidney (C: magnification 40 \times , D: magnification 200 \times) and that of the right kidney (E: magnification 40 \times , F: magnification 200 \times) were papillary renal cell carcinoma (PRCC) (type 1). Immunohistochemically, tumor cells of the left kidney were positive for p504s (G: magnification 200 \times) and EMA (H: magnification 200 \times)

trisomy or tetrasomy of chromosome 7 and 17, and the loss of chromosome Y in men, which are also detected in PRCC arising in ACDK [10]. Approximately 85% of ADPKD cases are caused by mutations of the PKD1 gene encoding polycystin 1, which is located within the cell membrane and is involved in cell proliferation and development. Dysfunction of polycystin 1 is considered to result in over-proliferation of tubular epithelial cells and altered cell polarity [11]. PKD1 was also reported to inhibit the mTOR signaling pathway and its activation in ADPKD [12]. However, there have been no reports of the association between PRCC and mTOR. Therefore, the genetic changes processing RCC in ADPKD requires further investigation.

Renal AML is known as a major manifestation of TSC caused by germ-line mutations of the TSC2 or TSC1 gene, and multiple or bilateral tumors were commonly seen in 80% of the renal cases [13]. Sporadic AML is also associated with TSC2 gene mutations [14]. PKD1 and TSC2 genes are generally considered to contribute to the pathogenesis of ADPKD and AML, respectively, and are located directly next to each other on chromosome 16p. PKD1/TSC2 contiguous gene syndrome caused by large mutation on both TSC2 and PKD1 in TSC patients is also reported to result in severe renal dysfunction [15]. Martignoni *et al.* reported two cases of PKD1/TSC2 contiguous gene syndrome with multiple AML in the bilateral kidneys with diffuse polycystic changes similar to ADPKD [15]. However, there have been only a few reports of renal AML occurring in ADPKD, and the association between ADPKD and AML has remained unknown [2]. To the best of our knowledge, case 1 is the first reported case of bilateral AML without any significant manifestations of TSC, and its clinical presentation is indeed different from that of PKD1/TSC2 contiguous gene syndrome. Therefore, further investigations are required to explore the pathogenesis of AML in ADPKD.

The authors declare no conflict of interest.

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