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CASE REPORT

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Unusual familial cystic kidney disease: combining fine radiologic and genetic evaluation to solve the case

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Abstract

Background Autosomal dominant polycystic kidney disease (ADPKD) is the most prevalent hereditary kidney disease, characterized by enlarged kidneys with numerous cysts, high blood pressure, and a variety of extrarenal complications. This disease is a significant cause of renal failure and requires accurate differentiation from other cystic kidney diseases, especially when family history does not clearly indicate ADPKD. This is crucial due to differences in prognosis, treatment, and familial implications. Advanced molecular genetics and imaging techniques are employed to diagnose and assess the prognosis of patients and their families.

Case presentation The case study revolves around three patients from the same family—two sisters and one daughter—referred to a nephrology department for ADPKD management. The initial proband, a 42-year-old woman, experienced abdominal discomfort leading to an ultrasound that suggested ADPKD. However, MRI findings indicated standard-sized kidneys with bilateral parapelvic cysts, and no genetic markers for ADPKD were found. Her sister, presenting with controlled hypertension and similar ultrasound findings, also had her initial ADPKD diagnosis refuted by MRI and genetic testing, which revealed no significant mutations. The daughter, however, exhibited a different scenario with enlarged kidneys and multiple cysts characteristic of early-stage ADPKD. Genetic testing confirmed a deleterious *PKD1* mutation, suggesting a de novo mutation, as her father showed no signs of the disease.

Conclusion This study highlights the complexity and necessity of thorough diagnostic processes in suspected ADPKD cases to prevent misdiagnosis. The initial symptoms and imaging might misleadingly suggest ADPKD, as seen in the cases of the two older patients. Still, further detailed imaging and genetic analyses revealed no ADPKD, preventing inappropriate treatment and stress. In contrast, the younger patient's distinctive clinical and genetic profile confirmed ADPKD, illustrating the variability within even closely related individuals. Such detailed assessments are crucial in guiding correct treatment decisions and providing accurate familial counseling, emphasizing the importance of considering a broader spectrum of renal cystic disorders before confirming a diagnosis of ADPKD.

Keywords Kidney, Cysts, Polycystic kidney, Autosomal dominant, Mutation

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Background

Autosomal dominant polycystic kidney disease (ADPKD) is the most prevalent hereditary kidney disease and remains one of the leading causes of renal failure. The condition presents various clinical features, including enlarged kidneys due to proliferating cysts, high blood pressure, and a range of extrarenal complications. Molecular genetics and imaging techniques are tools to diagnose and prognose individual patients and their families [1]. Understanding the differential diagnoses among cystic kidney diseases is essential, especially in cases where family history is unclear. This differentiation is necessary due to the disparities in prognosis, treatment, and familial implications [2]. The following case study details the clinical trajectories of three related patients referred to our specialized center for ADPKD management who turned out to have different diseases.

Case presentation

Three patients, namely the proband (II-2), her sister (II-3), and her daughter (III-2), were referred to the Nephrology Department of our university hospital by their shared primary care physician for the management of suspected ADPKD.

Patient II-2 (proband)

In the case of the 42-year-old woman (II-2), abdominal discomfort prompted an abdominal ultrasound (US) that revealed multiple bilateral hypoechoic structures suggestive of ADPKD. The patient had no family history of kidney disorders, prior medical history, or high blood pressure. No proteinuria or hematuria was noted, and her estimated glomerular filtration rate (eGFR) was normal (106 ml/min/1.73 m2). Subsequent MRI aimed at renal volumetry displayed standard-sized kidneys (10.7×5.7 cm on the right and 11.6×6 cm on the left). Our radiology center, genitourinary specialized, later suggested bilateral parapelvic cysts without cortical cysts rather than typical ADPKD features (Fig. 1). Furthermore, there were no liver cysts.

Patient II-3

The patient's sister, aged 38, had arterial hypertension diagnosed at age 35 and successfully managed with a calcium channel blocker. Her medical history remained unremarkable, without urological symptoms. The abdominal US, conducted after her sister's diagnosis, also revealed kidneys with hypoechoic lesions and a hepatic cyst. The attending physician drew parallels to ADPKD in her case as well. During her initial visit to our center, the physical examination yielded no anomalies and normal blood pressure (127/85 mmHg). Laboratory results indicated normal renal function (eGFR 107 ml/min/1.73 m2), a normal urine protein to creatinine (UPC) ratio of 0.1 g/g, and the absence of microscopic hematuria. Renal MRI corroborated normal-sized kidneys (10.2×5.3 cm on the right and 11.3×6 cm on the left) but characterized the cysts as parapelvic cysts, a banal solitary hepatic cyst measuring 10 mm was present in segment VII (Fig. 1). This MRI invalidated the diagnosis of ADPKD yet again.

Both patients underwent genetic testing for a panel of cystic kidney diseases genes comprising *PKD1*, *PKD2*, *GANAB*, *HNF1b*, *SEC63*, *PRKCSH*, and *UMOD*. Nevertheless, no deleterious variants were identified. No signs

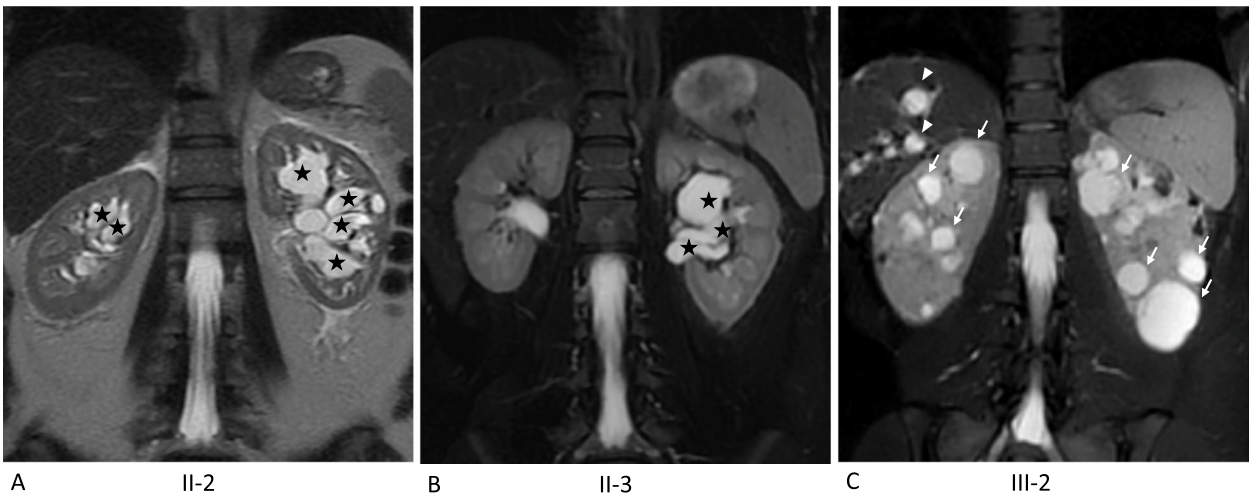

Fig. 1 Comparative MRI Findings in Patients with Parapelvic (Patients II-2 & II-3) vs ADPKD (Patients III-2). Coronal T2-weighted fat-suppressed (fat sat) MRI images demonstrate the presence of bilateral parapelvic cysts (black stars) without any accompanying cortical cysts in Patients II-2 (**A**) and II-3 (**B**). In contrast, coronal T2-weighted fat-suppressed MRI images for Patient III-2 reveal bilaterally enlarged kidneys, multiple cortical cysts (white arrows), and associated liver cysts (white arrowheads) (**C**)

of Fabry disease (FD) were identified, and no history of renal failure, cardiomyopathy, or stroke was recorded in the relatives. Since no clinical features suggesting FD were identified in the 2 sisters with parapelvic cysts or in their parents, no genetic testing of the *GLA* gene was performed. Of note, neither their father (I-1) or mother (I-2) had renal cysts at age 65 and 66 years, respectively.

Patient III-2

The 21-year-old proband 's daughter's medical history was marked only by managed hypothyroidism (Levothyroxine, 50 µg per day). Her blood pressure and renal function (eGFR 120 ml/min/1.73 m2) were within normal ranges, without microscopic hematuria or proteinuria. She was referred to our center for familial screening. A kidney US unveiled slightly enlarged kidneys, measuring 12.8 × 5.4 cm on the right and 12.2 × 6 cm on the left, each housing more than ten cysts. A subsequent MRI confirmed the mostly cortical cysts, while parapelvic cysts were absent. Her height-adjusted total kidney volume (htTKV) was 352 ml/m. Three small hepatic cysts were also identified (Fig. 1).

Her renal imaging pattern aligned with ADPKD's early stages. Despite the lack of *PKD1* or *PKD2* mutations in her mother (II-2) and maternal aunt (II-1), next-generation sequencing (NGS) genetic testing was performed owing to her distinctive renal phenotype. The evaluation uncovered a deleterious mutation in the *PKD1* gene (c.11453dup in exon 41), confirming an ADPKD molecular diagnosis. In light of her mother's (II-2) absence of a renal ADPKD phenotype or *PKD1* mutation, attention turned to the paternal lineage. Her 42-year-old father had no history of hypertension, urological symptoms, or chronic kidney disease. A renal ultrasound conducted at age 42 showed no renal cysts, effectively ruling out a *PKD1* mutation. Patient II-2 thus had a *PKD1* de novo mutation (Fig. 2).

Discussion and conclusions

US findings are pivotal in ADPKD diagnosis, mainly when there is a positive family history [3, 4]. For individuals under 40, MRI is more accurate when a threshold of more than ten cysts for positive diagnosis is applied [5]; however, this diagnostic criteria is applicable only when another sibling has ADPKD. Standardized ADPKD diagnostic criteria for patients without a family history are currently lacking, placing genetic testing at the forefront for such cases, which reveals de novo mutations in half of these patients [6]. Most of these mutations are concentrated within the *PKD1* gene, with truncating mutations constituting roughly two-thirds.

Accurate ADPKD diagnosis is crucial for treatment decisions, such as Tolvaptan eligibility, which is FDA and EMA-approved for adults with rapidly progressive ADPKD as per MAYO and ERA-EDTA classifications [7]. These classifications consider various factors like age, eGFR, htTKV, which is the primary predictor of rapid progression to ESKR, and PROPKD score, taking into account the molecular diagnosis of a truncating *PKD1* mutation, linked to a more adverse renal prognosis [8]. Patient III-2 did not yet qualified for Tolvaptan despite her htTKV-based Mayo class IC and a *PKD1* truncating mutation predicting rapid progression, because of her young age, but she will go on follow-up. The PROPKD

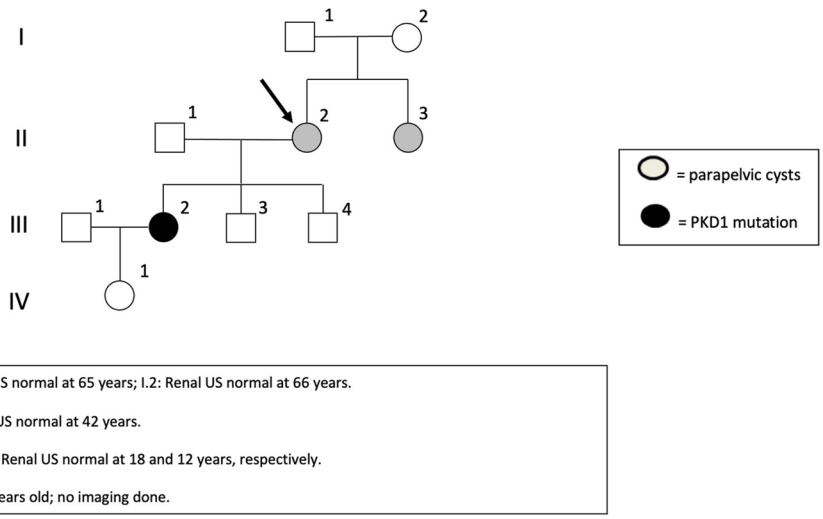

Fig. 2 Genealogical tree. Square: males; circles: females. Renal US normal at 65 years (I.1); renal US normal at 66 years (I.2); renal US normal at 42 years (II.1); renal US normal at 18 and 12 years (III.3 & III.4, respectively); 2 years old, ADPKD screening not performed (IV-1)

score is inappropriate for patients under 35 without complications, for whom htTKV and *PKD1* mutations primarily guide treatment.

Currently, octreotide long-acting release (octreotide-LAR), a somatostatin analog, is also approved in Italy for the treatment of ADPKD fast progressors. Somatostatin analogs have demonstrated efficacy not only in the treatment of ADPKD but also in polycystic liver disease [9].

Given the implications for prognosis and family, avoiding ADPKD misdiagnosis is equally crucial. This condition should not be confused with renal sinus cysts, benign simple renal cysts within the renal sinus, categorized as parapelvic or peripelvic cysts [10]. Parapelvic cysts originate from the renal parenchyma and protrude into the renal sinus [11], generally solitary or limited in number [12, 13]. Peripelvic cysts originate within the sinus, can be simple or multiloculated, and often manifest bilaterally and in multiple numbers. They stem from the cystic dilatation of lymph-filled cavities [14, 15]. Clinically, "renal sinus cyst" broadly describes any fluid-filled cyst within the renal sinus, as the specific type usually has minimal impact. They are frequently misdiagnosed as pyelocaliceal dilation on unenhanced CT scans or US due to their fluid-attenuated, hypoechoic nature [16], but interconnected calyces and a “cauliflower-like” renal pelvis can help to suggest hydronephrosis. Contrast-enhanced CT during the excretory phase distinguishes peripelvic cysts from hydronephrosis, as sinus cysts displace the enhanced collecting systems [12]. The prevalence of renal sinus cysts is between 1.5% and 6% of the older population [17, 18], less common than the 5.8% to 10% for simple cortical cysts [19].

Renal sinus cysts are usually asymptomatic and found incidentally, though larger cysts may cause obstruction by compressing the renal collecting system, negatively affecting renal function [20, 21]. Complications encompass cyst infection, chronic pyelonephritis, stone formation due to stasis [22], and intracystic bleeding. Renal pedicle compression from vascular sources might trigger renin-mediated hypertension [22]. Finally, renal sinus cysts could potentially obscure malignant lesions. Umemoto et al. demonstrated that three of 73 patients with renal sinus cysts had renal pelvic cancer, and another displayed ureteral cancer. Tumors could impair lymph flow, contributing to cyst development [23].

Importantly, FD patients face an elevated risk of developing renal sinus cysts [24]. In a cohort comprising affected carriers harboring classic and cardiac FD variants, the prevalence of renal parapelvic cysts was heightened (14.5% in males and 10% in female carriers), with earlier onset than in the general population [25]. FD patients may also experience limb-related lymphedema. Riccio et al. recently reported a case of a 30-year-old woman presenting with both renal cysts and parapelvic cysts; she was shown to carry both a *PKD1* gene variant (c.10549G > T) and a *GLA* gene variant (c.868A > C) [26]. No signs of FD in our patients II-2 and II-3 were identified, and no history of renal failure, cardiomyopathy, or stroke was recorded in the relatives making it very unlikely that they had FD related renal sinus cysts.

In conclusion, this study illuminates the potential pitfalls of hastily attributing familial renal cysts solely to ADPKD. A misdiagnosis can lead to inappropriate treatment strategies, undue stress, and inaccurate familial counseling. Hence, a holistic approach, including precise imaging and genetic assessment, is essential to diagnose and manage patients with cystic kidney diseases accurately. Clinicians must remain vigilant and consider the broader spectrum of renal cystic disorders, including renal sinus cysts, before settling on a definitive diagnosis of ADPKD.

Abbreviations

ADPKD	Autosomal Dominant Polycystic Kidney Disease
US	Ultrasound
eGFR	Estimated Glomerular Filtration Rate
MRI	Magnetic Resonance Imaging
UPC	Urine Protein to Creatinine Ratio
PKD1, PKD2	Polycystic Kidney Disease 1 and 2 genes
GANAB	Neutral Glucosidase Alpha AB
HNF1b	Hepatocyte Nuclear Factor 1beta
SEC63	SEC63 Homolog, Protein Translocation Regulator
PRKCSH	Protein Kinase C Substrate 80K-H
UMOD	Uromodulin
NGS	Next-Generation Sequencing
htTKV	Height-Adjusted Total Kidney Volume
FDA	Food and Drug Administration
EMA	European Medicines Agency
ERA-EDTA	European Renal Association-European Dialysis and Transplant Association
ESKR	End Stage Kidney Disease
PROPKD	Prediction of Polycystic Kidney Disease Progression
PI3K/AKT/mTOR	Phosphoinositide 3-Kinase/Protein Kinase B/Mammalian Target of Rapamycin Pathway
FD	Fabry Disease
GLA	Galactosidase Alpha

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Authors’ contributions
SB and RN analyzed and interpreted the patient data. SB performed the bibliography. SB and OH performed the radiological analysis. BK performed the work supervision. All authors read and approved the final manuscript.

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Availability of data and materials
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Declarations

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Yes; consent obtained from patients and their families.

Consent for publication
Patients and their families were informed of this publication, and they gave their informed consent.

Competing interests
The authors declare no competing interests.

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