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The prospect of novel orphan therapeutic protocol for *TSC2/PKD1* contiguous gene syndrome: a case report

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Abstract

Background Autosomal dominant polycystic kidney disease (ADPKD, OMIM # 601313, # 173900) and tuberous sclerosis complex (TSC2, OMIM # 191092, #613254) are inherited multisystemic diseases that rarely associate. Large deletion on chromosome 16 can result in *TSC2/PKD1* contiguous gene (deletion) syndrome (PKDTS, OMIM # 600273) presenting significant diagnostic and management challenges.

Case presentation A 50-year-old male presented clinical features consistent with autosomal dominant polycystic kidney disease (ADPKD) and signs of tuberous sclerosis complex (TSC), such as multiple facial angiofibroma, cortical tubers, cerebral hamartomas, and renal and hepatic angiomyolipomas, was investigated for the multisystemic disease pattern. Genetic testing confirmed the diagnosis of *TSC2/PKD1* contiguous gene deletion syndrome (PKDTS), leading to the initiation of tolvaptan treatment to reduce the progression of ADPKD and considering everolimus as a potential therapeutic solution to decrease the size of angiomyolipomas, thereby minimizing the risk of spontaneous bleeding. Our report underlines for the first time, up to our knowledge, that the proposed therapy protocol for *PKD1/TSC2* contiguous gene deletion syndrome could have potential.

Conclusions This case illustrates the importance of recognizing overlapping genetic disorders, and providing insights into an innovative therapeutic approach. By integrating detailed clinical assessment with genetic testing, the diagnosis was clarified, and targeted therapies can be selected to address the dual impact of ADPKD and TSC; however, further studies are needed to evaluate the efficacy and safety of this approach. We also emphasize the need to recognize other cases of renal polycystic disease associated with angiomyolipomas and cutaneous manifestations.

Keywords Case report, *TSC2/PKD1* contiguous gene deletion syndrome (PKDTS), Autosomal dominant polycystic kidney disease (ADPKD), Tuberous sclerosis complex (TSC), Tolvaptan therapy, Everolimus therapy, Angiomyolipomas (AML), Genetic testing

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Background

Autosomal dominant polycystic kidney disease (ADPKD) is an inherited multisystemic condition, characterized by polycystic features, mostly located in the kidneys, but also in other organs as the patient could exhibit non-polycystic manifestations such as cerebral aneurysms, cardiac valve abnormalities, etc [1]. It is the fourth leading cause of end-stage renal disease globally [2]. Tuberous sclerosis complex (TSC) is an autosomal dominant disorder that affects multiple organs, including the brain, heart, skin, liver and kidney. The disease appears secondary to a mutation in a suppressor gene – *TSC1* or *TSC2*. Individuals can express benign tumors called hamartomas in numerous organs, but in the kidneys, the patients can develop cysts and/or angiomyolipomas (AML), mostly in the setting of *TSC2* gene mutation [3].

ADPKD is caused by mutations in either *PKD1* or *PKD2* genes. *PKD1* is located on chromosome 16, at position 16p13.3. *TSC2* is also located on chromosome 16, lying immediately adjacent to *PKD1*. Large deletion can result in *TSC2/PKD1* contiguous gene deletion syndrome [4], leading to severe symptoms and worst kidney prognosis [5].

It is well-known that Tolvaptan a vasopressin V2-receptor antagonists has been explored in ADPKD patients alone, due to their capacity to reduce the total kidney volume growth, and the decline in kidney function over different periods [6, 7]. The positive effect of Tolvaptan in decelerating the progression of ADPKD in later stages (referring to individuals aged 18–55 years with an eGFR of 25–65 mL/min/1.73 m^2 or those aged 56–65 years with an eGFR of 25–44 mL/min/1.73 m^2) was demonstrated in a phase 3, multicenter, randomized, double-blind, placebo-controlled study. This analysis included 1370 patients and displayed a slower decline in the estimated GFR after one year of follow-up [6].

Currently, the effect of tolvaptan has been also explored in *TSC2/PKD1* contiguous gene syndrome patients, as described, for example by Guerra-Torres case report [8]. The study describes the case of an asymptomatic patient with *TSC2/PKD1* contiguous gene syndrome treated with tolvaptan for 12 months. The patient's blood pressure improved and tolvaptan was considered to be safe and well tolerated, but as concluded by the author, more extensive studies are needed to understand its implications in this rare associated disease. In another study, the case of an 11-year-old girl with *TSC2/PKD1* contiguous gene deletion syndrome with rapid renal cyst enlargement treated with tolvaptan was reported [9]. 12 months after the introduction of tolvaptan the height-adjusted total kidney volume rate decreased from 37 to 3% and renal cyst enlargement was attenuated without major adverse events. In 2010, 433 patients with ADPKD received either placebo or the mTOR inhibitor everolimus over 2 years in a double-blind trial [10]. The total kidney volume increase (defined as the primary outcome) was reduced based on magnetic resonance imaging measurements at 12 and 24 months, but the progression of renal impairment in ADPKD patients was not decreased after the everolimus therapy.

However, the PKDTS patients not only have ADPKD but also typical TSC manifestations. mTOR (mammalian target of rapamycin) inhibitor everolimus represents the treatment choice for *TSC2/PKD1* contiguous gene syndrome patients as it reduces the cyst growth and moderates total kidney volume, as described by the recent case series study on 4 children by Orosz et al. [11]. Despite advances in managing ADPKD and TSC individually, there is a lack of established therapeutic protocols for the treatment of *PKD1*/*TSC2* contiguous gene deletion syndrome in nephrology. In this context, could the combined use of these two therapies serve as a viable treatment model for managing *PKD1*/*TSC2* contiguous gene syndrome? While each drug targets distinct aspects of the disease, their concurrent use in this unique genetic context requires further investigation to fully understand the therapeutic potential and limitations.

In this study, we report the case of a 50-year-old man with suspected *TSC2/PKD1* contiguous gene deletion syndrome, who was placed on tolvaptan treatment for ADPKD. Based on the genetic findings, the initiation of dual therapy, including everolimus to address the tuberous sclerosis manifestations, is currently under consideration as a potential future option.

Case presentation

A 50-year-old man with a past medical history of ADPKD and hypertension was admitted to the emergency department of the hospital for an intense headache, being suspected of a ruptured cerebral aneurysm.

The clinical examination noticed multiple angiofibromas located at the nasolabial fold (Fig. 1) and elicited bilateral lumbar tenderness. All images from this study are part of the Clinical Hospital C.I. Parhon Iasi collection.

A cerebral CT scan infirmed the presence of an aneurysm but, described multiple hypodense lesions. A subsequent MRI investigation identified cortical tubers, as presented in Fig. 2, where T1 native axial shows in green a hypo intense lesion, located in the right and left frontal lobe, cortically and modifying the aspect of the gyri. Also, the ADC sequence shows high intensity at the same lesion, suggestive of cortical tubers.

Figure 2 shows also the radiological aspect of cortical cerebral hamartoma, illustrating a nodular lesion located periventricular with a hypo-dense signal in SWI sequence (E. MRI) and the calcified periventricular lesion (F. CT scan).

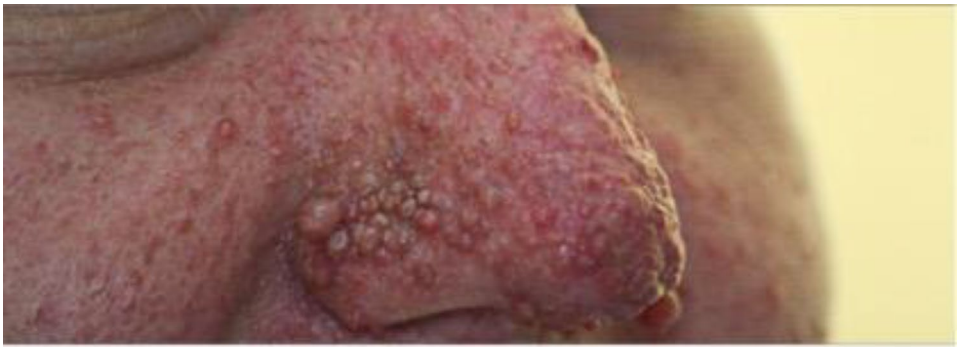

Fig. 1 Multiple nodular lesions located at the nasolabial fold with an erythematous aspect resembling a severe form of acne

Figure 2G presents the multiple renal cysts located bilaterally, suggestive of ADPKD in a CT scan of renal angyomyolipoma.

Laboratory tests showed an elevated serum creatinine of 2.21 mg/dL, similar to the evaluation made 8 months before, suggesting chronic kidney disease. Abdominal ultrasound revealed multiple bilateral renal cysts, consistent with adult PKD [12].

The multiple facial angiofibromas, cortical tubers, and cerebral hamartomas were not typical for ADPKD, suggesting tuberous sclerosis. An abdominal CT scan identified multiple renal cysts, with a total kidney volume of 3671.8 mL, and revealed 2 AML, one in the liver and one in the right kidney; the renal angiomyolipoma measured 51/42/48 mm.

To further clarify the diagnosis, genetic testing results were obtained externally from Blueprint Genetics, Finland, using the FLEX Cystic Kidney Disease Panel Plus and next-generation sequencing (NGS) technology. The analysis confirmed a heterozygous deletion (seq[GRCh37] del(16)(p.13.3) chr16:g.2034159_2148045del), affecting exons 31–46 of *PKD1* and the entire *TSC2* gene (Fig. 3). This result provided certainty for the diagnosis of *TSC2/PKD1* Contiguous Gene Syndrome. The pedigree diagram of the genetic screening is presented in Fig. 4.

Regarding the origin of the pathogenic genetic alteration, no cases of cystic kidney disease or tuberous sclerosis were reported in the parents or other immediate family members, suggesting that the mutation may represent a de novo event in the proband. However, this cannot be determined with certainty due to the history of hypertension in the father of the proband, died at the age of 55, which could potentially indicate an undiagnosed manifestation of ADPKD.

The patient received genetic counseling, and his two children were called in for screening, as the disease follows an autosomal dominant inheritance pattern, with a 50% risk of inheriting the mutation for each offspring. As stated by the patient, his daughter is very likely to have the condition, as she exhibits cutaneous facial lesions similar to his own. Clinical and genetic evaluation of the children is currently pending (at the time of this report).

Regarding the treatment, the initial antihypertensive medication was adjusted to achieve optimal blood pressure control. Pathogenic treatment with tolvaptan was initiated to slow cyst growth and preserve kidney function in ADPKD at a creatinine value of 2.21 mg/dL. Three months later, the patient was in a clinically stable condition, with normal liver function and serum creatinine levels of 1.99 mg/dL and 2.05 mg/dL at the 1- and 3-month follow-up periods, respectively, as illustrated in Fig. 5. Following the confirmation of the genetic diagnosis, the addition of everolimus therapy was considered as a potential future option to address the angiomyolipomas associated with tuberous sclerosis and to mitigate the risk of spontaneous bleeding.

Discussions

TSC is a rare condition that could overlap with another genetic kidney disease, ADPKD, most of these rare reported cases being pediatric ones [13]. About 20% of TSC patients develop kidney cysts, but only 2% overlap with ADPKD [8, 14], resulting in combined morbidity and therapeutic needs.

The benefit of using Tolvaptan, a vasopressin V2-receptor antagonist, to slow down the progression of CKD in ADPKD is demonstrated [15]. Since the patient had a total kidney volume of 3671.8 mL (Mayo 1D) and an eGFR of 33 mL/min/1.73m^2 (CKD-EPI), the criteria to start the Tolvaptan treatment were fulfilled. This therapeutic decision was also favored by the results of the Guerra-Torres study, mentioned in the background, that noticed the good tolerance of Tolvaptan in *TSC2/PKD1* contiguous gene deletion syndrome and the improvement in blood pressure control [8]. As far as we know, this is the only case closely similar to ours published in the literature, describing an asymptomatic 33-year-old Spanish male diagnosed with TSC2/PKD1 contiguous gene syndrome and CKD stage 3b. The creatinine level in this study showed a slight deterioration in renal function from 2.11 mg/dL to 2.48 mg/dL after 12 months of

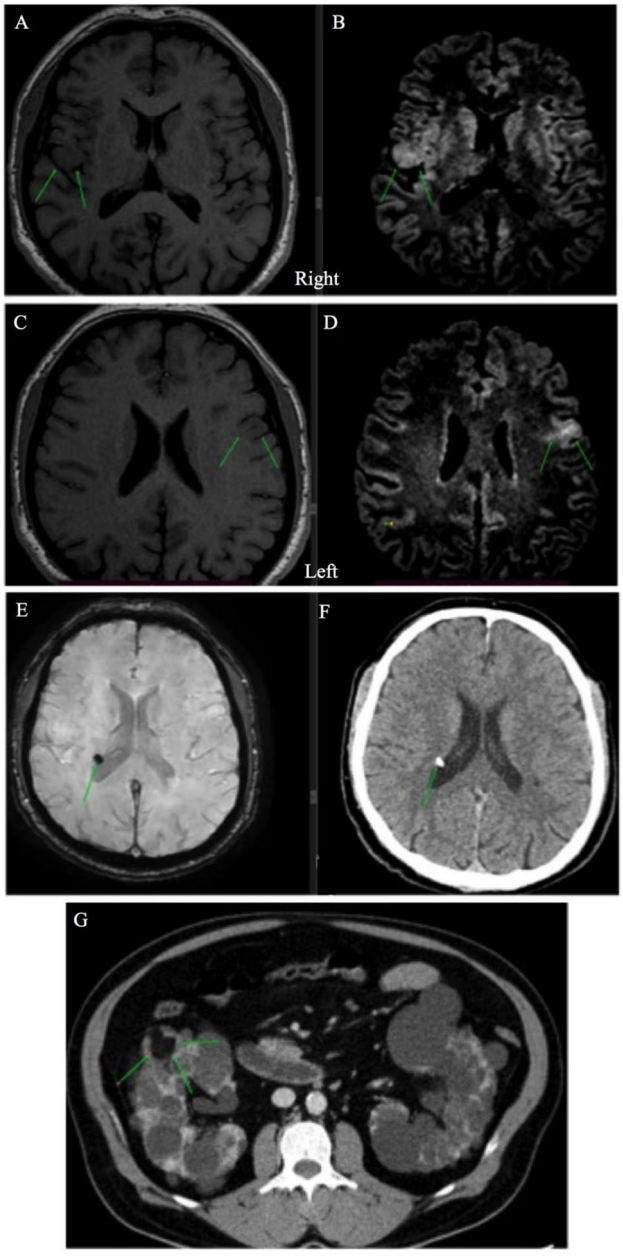

Fig. 2 MRI aspect of cortical cerebral tubers- axial slices; T1 native axial in the (**A**) right and **C** left frontal lobe; (**B**) and **D** ADC sequence; **E** MRI aspect of a nodular lesion located periventricular with a hypo dense signal in SWI sequence and **F** CT scan in axial plane showing the calcified periventricular lesion marked by the green arrow; **G** CT aspect of renal angyomyolipoma-axial slices; the green arrows in the right kidney present a high hypo-dense lesion with an irregular border suggestive of angiomyolipoma

treatment. The study did not include follow-up CT imaging to analyze kidney volume. The renal function of our patient during the follow-up period in relation to this study is shown in Fig. 5.

An important issue of the presented case is the AML, a benign vascular tumor, with a significant risk of spontaneous rupture and a potentially life-threatening hemorrhage. Treatment with everolimus, provides a promising approach to diminish the size of the AML, thus reducing the risk of spontaneous bleeding [16, 17]. Regarding the surgical treatment of a large-size AML, the urological decision for the reported patient was active surveillance, delaying any invasive procedure. This opinion was supported by studies that did not confirm the previously considered relationship between the size of the AML and the risk of spontaneous rupture [18] and promotes the nephron-sparing attitude in a patient with CKD.

There are also considerations regarding the presence of an aneurysm inside the AML, as the size of the aneurysm > 5 mm associated a higher risk of spontaneous rupture. Nowadays, the first line of active treatment is the selective arterial embolization that should be performed in symptomatic patients, in those with an aneurysm > 5 mm inside the AML, in cases with rapid growth rate, and pregnant women [19]. This is the reason why a selective angiography was recommended to identify and measure the eventual aneurysms to provide the vascular mapping of the kidney and, if a selective arterial embolization will be required for the reported patient.

However, the implementation of an active surveillance attitude is dependent on multiple factors (the size of the AML, the associated aneurysm, the rate of AML growth, and the pregnancy).

A key aspect of this case is the hereditary nature of *TSC2/PKD1* contiguous gene deletion syndrome, emphasizing the importance of family screening and early genetic counseling to identify at-risk relatives. The diagnosis of this syndrome in our patient strongly suggests the possibility of its presence in at least one offspring, who exhibits similar facial lesions. Early detection is crucial for initiating timely management strategies and preventing severe complications while enhancing the understanding of disease variability. Furthermore, this case underscores the need for clinicians to recognize subtle familial signs that can guide the diagnostic process in genetic conditions.

The case report presents several limitations that should be considered. First, as a single case study, the ability to generalize the findings to a broader population is limited. Additionally, the proposed dual therapy, combining tolvaptan and everolimus, has not yet been fully initiated, and clinical outcomes are currently unavailable. The potential benefits and risks of combining these treatments remain uncertain, and the decision to initiate everolimus therapy is still under careful evaluation, given the novelty of this approach and the lack of precedent in the medical literature. The third, the follow-up period of three months is limited, and therefore insufficient to evaluate the long-term efficacy of tolvaptan in our patient.

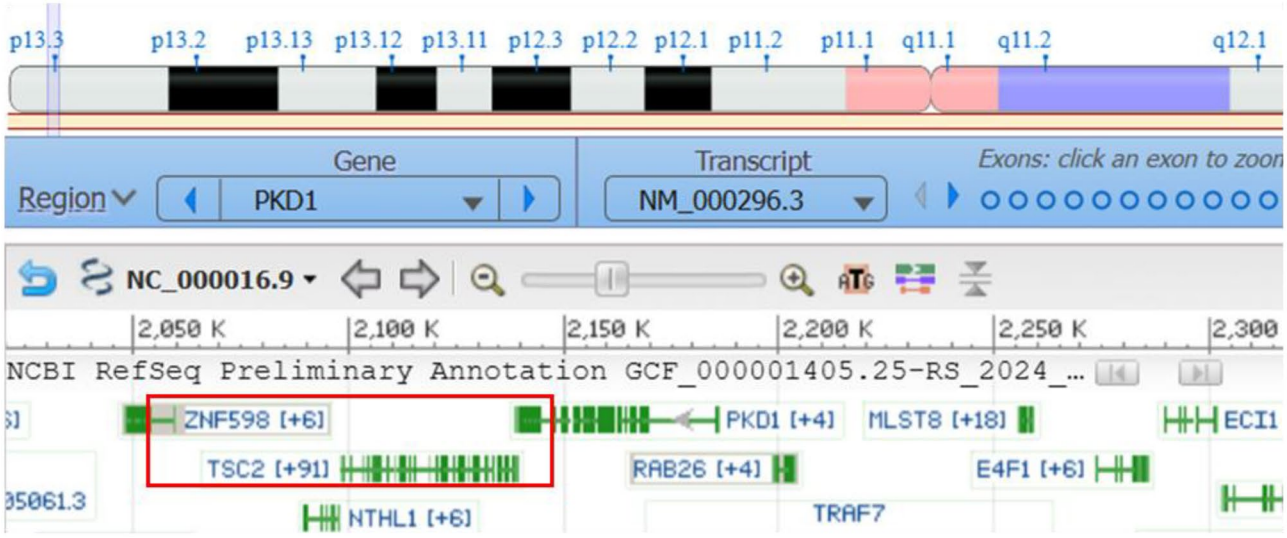

Fig. 3 Schematic representation of the chromosome 16 deletion encompassing *PKD1* and *TSC2* genes; the red box indicates the deletion, affecting exons 31–46 of *PKD1* and the entire *TSC2* gene. Image obtained from NCBI Genome Data Viewer (https://www.ncbi.nlm.nih.gov/gdv/)

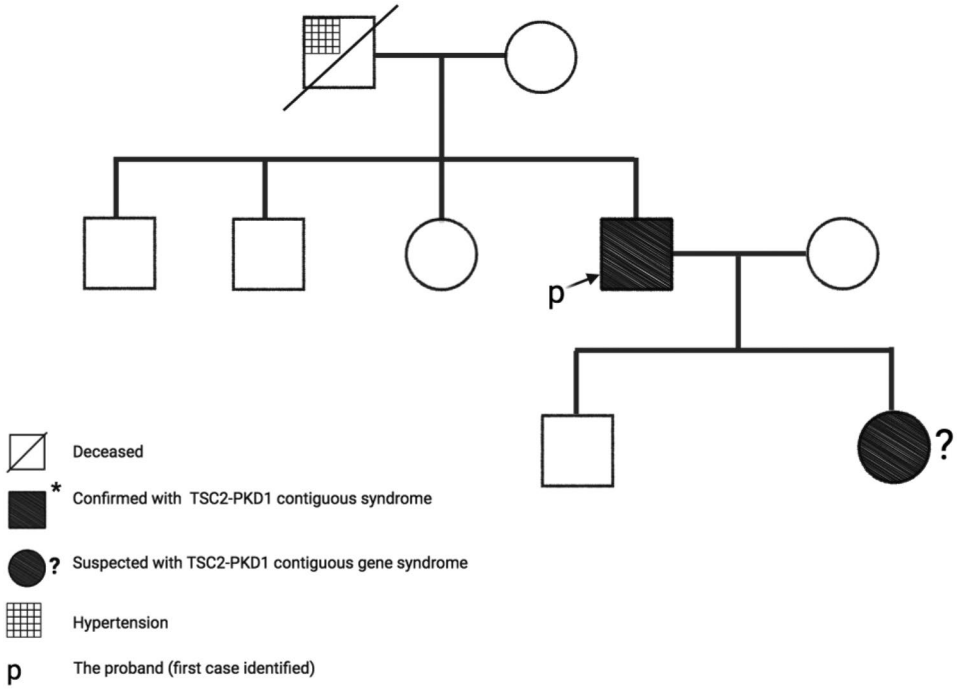

Fig. 4 The pedigree diagram

Conclusions

This case underscores the potential of a novel therapeutic approach combining tolvaptan and everolimus for *TSC2/PKD1* contiguous gene deletion syndrome, highlighting the importance of genetic testing in guiding treatment decisions and the need for further research to validate this strategy.

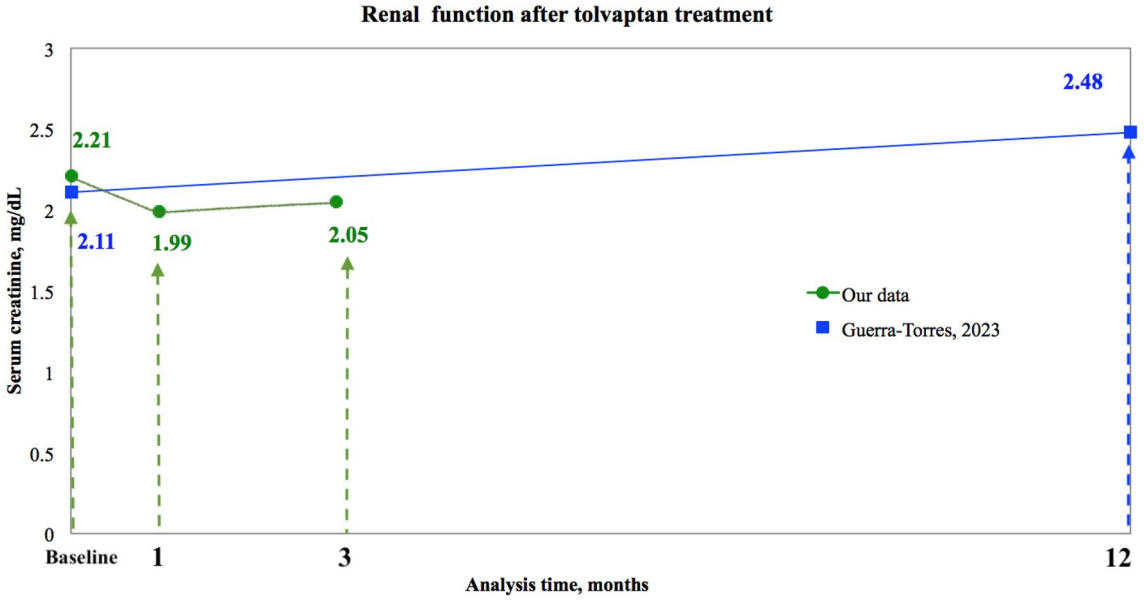

Fig. 5 Renal function after Tolvaptan treatment

Abbreviations

PKDTS	TSC2/PKD1 Contiguous gene syndrome
ADPKD	Autosomal Dominant Polycystic Kidney Disease
TSC	Tuberous Sclerosis Complex
AML	Angiomyolipomas

Author contributions

BDA analyzed and interpreted the clinical data and performed the clinical evaluation of the patient. He contributed substantially to the conception and design of the study and was a major contributor to drafting and revising the manuscript. RCC contributed significantly to the conception and design of the study and performed the final manuscript revision. RGB and SR were responsible for the genetic analysis and interpretation, contributed to drafting the section on genetic diagnosis and disease presentation and ensured the accuracy and revision of the manuscript. GD contributed substantially to the conception and design of the study, conducted the literature review, and performed the final manuscript revision. ACC provided general supervision of the study, coordinated among research teams, and performed a critical review of the manuscript. ILM contributed substantially to the conception and design of the study, drafted and wrote the manuscript, conducted the literature review, and performed the final manuscript revision. All authors read and approved the final manuscript.

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Data availability

The genetic testing data referenced in this study were generated by Blueprint Genetics as part of routine clinical diagnostics. Due to patient confidentiality, these data are not publicly available; however, anonymized details can be provided by the corresponding author upon reasonable request or accessed directly by contacting Blueprint Genetics, in accordance with laboratory policies. Other datasets supporting the findings of this study are available from the corresponding author upon request.

Declarations

Ethical approval

Ethical approval for this study was obtained from the Ethics Committee of the Grigore T. Popa University of Medicine and Pharmacy (no.394/2024.02.01), Iași, Romania. The study was conducted in accordance with the ethical standards of the institutional research committee and the 1964 Helsinki Declaration and its later amendments. Written informed consent was obtained from the patient for participation in this study.

Consent for publication

Written informed consent for publication, including the use of anonymized patient data and images, were obtained from the patient.

Competing interests

The authors declare no competing interests.

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