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Autosomal Dominant Tubulointerstitial Kidney Disease: A Rare Case Report

Dr. D.R. Nivetha*[1], Dr. T.K.V. Sharavanan[2], Dr. T. Balaji[3], Dr. C. Prabaharan[4]
[1]Junior Resident, [2]Professor, [3]Assistant Professor, [4]Senior Resident,
[1,2,3]Department of General Medicine, [4]Department of Orthopaedics,
Tagore Medical College and Hospital, Chennai.

***Corresponding Author:**
Dr. D. R. Nivetha
Junior Resident, Tagore Medical College and Hospital, Rathinamangalam, Chennai-600127

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Abstract

Introduction:

ADTKD (Autosomal Dominant Tubulointerstitial Kidney Disease) is a group of rare genetic disorders characterized by tubular damage and interstitial fibrosis in the absence of glomerular lesions. Causes are due to mutation in genes: UMOD, REN, MUC-1, and HNF1B.

Case Discussion:

Here, we present a case of a 31-year-old male patient with a strong family history of chronic kidney disease, diagnosed with ADTKD. His clinical features were normal blood pressure, Progressive loss of kidney function, Bland urinary sediment, Mild albuminuria, and Normal kidneys on ultrasound with a family history suggestive of autosomal dominant inheritance. Histological findings were interstitial fibrosis and tubular atrophy with immunofluorescence negative for all antisera (IgA, IgG, IgM, C3, C1q, Kappa and lambda chains).

Conclusion: Presently, ADTKD has no specific therapies; and recommendations in this setting are based on limited evidence. Its management majorly relies on management of CKD, by following patient care guidelines for the same.

Keywords: Autosomal Dominant Tubulointerstitial Kidney Disease, early onset end-stage renal diseases, genetics of ADTKD

Introduction

Autosomal dominant tubulointerstitial kidney disease (ADTKD) presents itself as a rare, frequently missed, cause of end stage kidney disease (ESRD). It was proposed by KDIGO in 2015 (1-4), with presence of pathogenic variants in at least 5 different genes: uromodulin (UMOD), mucin 1 (MUC1), hepatocyte nuclear factor 1 beta (HNF1B), renin (REN), and the alpha subunit of the endoplasmic reticular membrane (SEC61A1) as its main cause. It is hence differentiated, into ADTKD-UMOD, ADTKD-MUC1, ADTKD–REN, ADTK D-HNF1B, ADTKD-SEC61A1 or ADTKD-NOS (not otherwise specified), accordingly, depending upon the affected gene (1-3); out of which ADTKD-UMOD and ADTKD-MUC1 are the most commonly identified variants (1, 2).

ADTKD can be categorized into 3 main subcategories, namely: ADTKD-UMOD: associated with high prevalence of adolescent gout, and is caused by mutations in the UMOD gene encoding uromodulin (Tamm-Horsfall glycoprotein); ADTKD-MUC1 caused by mutations in the MUC1 gene encoding mucin1; and ADTKD-REN- associated with signs of relative hyporeninaemia caused by mutations in the REN gene that encodes rennin (5). Autosomal dominant tubulointerstitial kidney disease (ADTKD) is associated with three major attributes: autosomal dominant inheritance, slowly developing chronic kidney disease (CKD), along with a bland

urinary sediment (6). All forms ADTKD presents with slowly developing CKD. However, a broad range is noted in this disease with some patients presenting with kidney failure in their teens (although rarely), while other patients in the same genetic make-up may not develop kidney failure until the age of 80 years (7). Although patients suffering from ADTKD rarely develop kidney failure in childhood, CKD is often prevalent. Hence, it is stipulated that the most important findings of ADTKD are autosomal dominant inheritance, slowly developing chronic kidney diseases, and bland urinary sediment.

There are various ways of diagnosing ADTKD, the minimal criteria for clinical suspicion of ADTKD is a conclusive family history of progressive chronic kidney disease (CKD) along with bland urine sediment, absence of notable proteinuria, and the presence of normal or small-sized kidneys. Histological findings are non-specific, including interstitial fibrosis and tubular atrophy. It may show thickening and lamellation of the tubular basement membranes and tubular dilatations (8, 9). The environmental and/or genetic factors adding to this variability are mostly unknown and the rate of kidney function decline is highly variable in most ADTKD subtypes (10, 11). Genetic examination should be considered as the primary diagnostic strategy, as a certain diagnosis requires identification of mutation in at least one of the known genes (2). However, absence of a mutation does not conclude absence of ADTKD as identification of additional loci is required, nevertheless. (4)

Some patients develop medullary renal cysts between the ages of 20 years and 80 years, with majority of the patients requiring renal transplant between the ages of 30-50 years (2). Research lacunae (like for most rare diseases) is because of low patient numbers and clustering of cohorts, hampering clinical and genetic characterization of ADTKD. However, in the past years due to the contribution of large international studies, there have been breakthrough novel insights, in studies related to ADTKD subtypes (12, 13).

Here, we present a case of 31-year-old male patient with a strong family history of chronic kidney disease, diagnosed with ADTKD.

Case Report:

This thirty-one-year male was incidentally found to have renal failure during his master health check up with a strong family history of chronic kidney diseases. At the time of presentation, on repeated blood pressure measurement his blood pressure was (130/80 mm Hg constantly). Pedigree analysis (figure-1) of the patient showed three members of the family deceased due to end-stage renal diseases and his father is currently on hemodialysis for the past eight months. Clinical examination showed pallor. Renal function tests showed urea of 40.3 mg/dl and creatinine of 2.2 mg/dl. Urinalysis showed bland urinary sediments with albumin 1+. Ophthalmoscopy was completely normal, as was a routine chest X-ray. Renal ultrasound demonstrated Right kidney: 10.4 x 3.9 cm cortical echoes increased with poor corticomedullary differentiation and the Left kidney: 10.3 x 4.6 cm cortical echoes increased with corticomedullary differentiation maintained. A kidney biopsy was done and it showed interstitial fibrosis and tubular atrophy of 30-40 percent of the core (figure-2). Immunofluorescence negative for all antisera (IgA, IgG, IgM, C3, C1q, Kappa and lambda chains). Genetic testing is the gold standard for the diagnosis of ADTKD.

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Figure 1: pedigree analysis

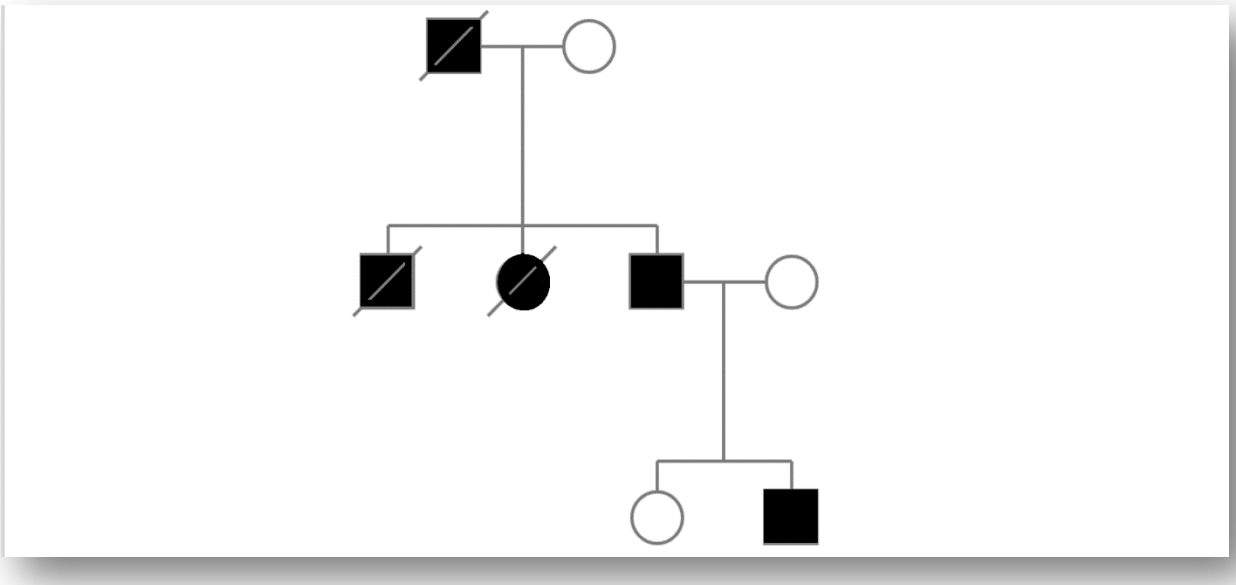

Figure 2: histology showing interstitial fibrosis and tubular atrophy

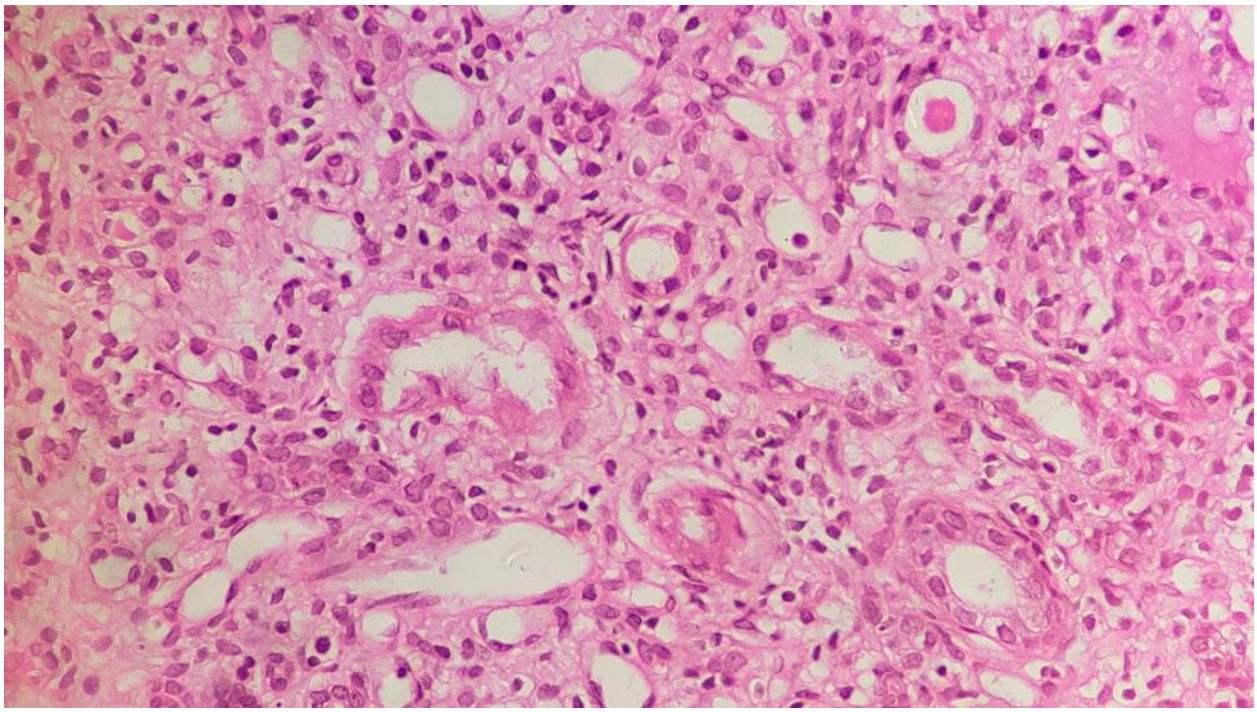

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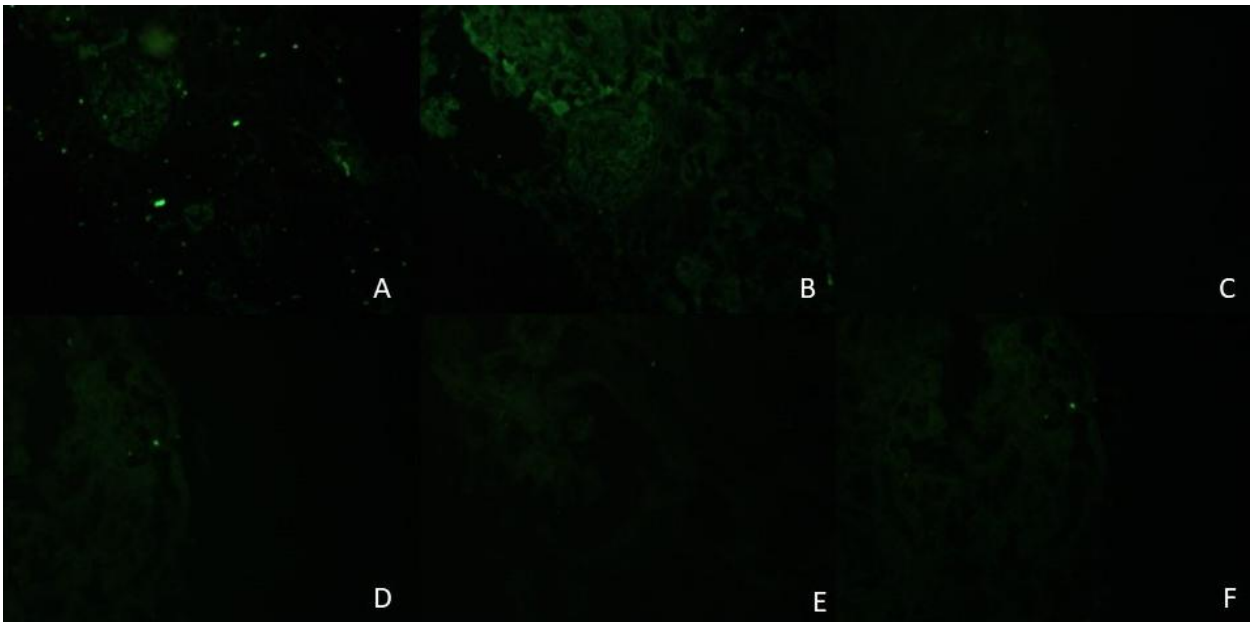
Figure 3: Immunofluorescence negative for all antisera



Discussion

In the present case, the patient had three members in his family with a history of CKD. Owing to his clinical presentation and laboratory results, ADTKD was the clinical diagnosis. The kidney biopsy revealed signs of interstitial fibrosis and tubular atrophy in 30-40% of the core. Immunofluorescence was negative for all antisera (IgA, IgG, IgM, C3, C1q, Kappa, and lambda chains). Based on the laboratory and clinical findings and with a strong family history of chronic kidney disease(CKD), ADTKD was confirmed.

The pathogenesis of ADTKD involves a wide spectrum of disruptions. Disease presentations are subservient to toxic gain-of-function effects, as the UMOD-deficient mice do not develop tubulointerstitial kidney disease and the UMOD gene is not under obvious constraint for predicted loss-of-function variants (4). The data retrieved in different cell lines and mouse models reiterates impaired trafficking of mutant UMOD, with endoplasmic reticulum (ER) accumulation and reduced urinary levels as the major molecular defect (14). Also, mutant UMOD that escapes ER quality control produces extracellular aggregates at the plasma membrane rather than wild-type polymers (15). There is more research required to understand the links between ER accumulation and tubulointerstitial fibrosis. Different branches have been implicated in vivo and in vitro as ER stress brings about the unfolded protein response (UPR) (16). The presence of ER stress has also been found in human kidneys. However, data from in vitro and in vivo studies do not match, in terms of finding a link to increased apoptosis (17) Where In vivo studies have shown Inflammatory reaction preceding fibrosis (18) along with secondary mitochondrial dysfunctions as well as impaired energy homeostasis (19). There is evidence of overall TAL dysfunction along with reduced expression of sodium–potassium–chloride (Naþ–Kþ–2Cl) co-transporter (NKCC2), when studied using mouse and human tissue (20).

The patient's pedigree analysis showed that three members of the family deceased due to end-stage renal diseases and his father is currently on hemodialysis for the past eight months. Studies show that even though there is a positive family history in ADTKD, because of the high mortality rate before disease presentation and/or inconsistent rate of disease development and progression, the disease may not be diagnosed in all family members, even when the majority of family members are involved (2).

The renal biopsy showed interstitial fibrosis and tubular atrophy in a wide section of its core. Previous studies have shown similar outcomes. For example, on histological examination, the renal area shows interstitial fibrosis with tubular atrophy, but normal glomeruli as well as induration and lamellation of tubular basement membranes, which is a rather

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frequent finding (21, 22). On various occasions, Tubular dilatation has been known to occur and tubular microcysts have been reported, as well. However, such findings were absent in our patient. The Immunofluorescence testing for complement and immunoglobulins is generally found to be negative which is in accordance with the present case (2).

In Ireland, the prevalence of CKD is about 11.8% (23) with more than 4400 people (approximately 928 per million) having ESRD (24). Patients with unspecified tubulointerstitial kidney disease were more likely to have a family history of kidney disease than those with other causes of CKD. A whole exome sequencing of 114 Irish families with CKD, showed a monogenic cause of CKD in a total of 37% (25). The Genetic causes of CKD, like Autosomal dominant polycystic kidney disease and Alport syndrome have been described in the Irish population, in the past as well (16); and, presently the Irish Kidney Gene Project (IKGP) has summed that nearly 34% of patients attending Irish nephrology units have a plausible family history (26). It shows that past family history of CKD is a significant risk factor for the occurrence of ADTKD.

Studies have mentioned other presentations of this disease including a normal kidney size initially, that declines with advancing age along with renal cysts of varying number and size, with their frequency being no higher than in 'non-cystic' kidney diseases (22). The cysts however, does not cause decline in glomerular filtration rate, and are found in advanced stages, as compared to early stages. Out of all forms of inherited CKD, ADTKD-UMOD, was the most common, after ADPKD, in a UK single centre study, showing a prevalence of 1% in stages 3-5 of chronic kidney disease, and 2% in patients with ESKD (3). UMOD mutation of 0.3% was seen with mostly ESKD in a WES test (whole exome sequencing) in a cohort of >3000 subjects, while 3% of all subjects displayed a monogenic diagnosis (28). The progression of CKD is subjected to variance, both inside and between families. Generally, the stage of ESKD is reached at an average age of 47 years with its range between 18–87 years (29). Common features of affected subjects included progressive CKD, bland urinalysis, normal and/or marginally increased blood pressure and normal or small sized kidneys. The clinical picture in individuals with advanced disease may be misleading, as secondary FSGS and subnephrotic proteinuria have been demonstrated (28). Generally, an autosomal dominant inheritance is characteristic, however, de novo UMOD mutation cases have been noted as well (17). In the present case, the patient had a high blood pressure of >160/>90 mm Hg constantly, although he was hemodynamically stable. Routine blood tests showed a strongly elevated serum creatinine. Urinalysis showed albuminuria.

Following is a case of a 12-year-old boy with a clinical presentation of polyarthritis, hyperuricaemia and tophi. Family history showed 8 affected individuals wherein the male proband's older brother suffered from gout from the age of 17, while his mother suffered from gout, along with stage 4 CKD from the age of 38 (30). Proband's renal biopsy sections, when studied under light microscopy reflected that one-in-six glomeruli had global sclerosis and extensive tubular atrophy. Similar to the present case where the patient had six globally sclerotic glomeruli with tubular atrophy. Additionally, direct immunofluorescence staining was negative for immunoglobulin and complement similar to the present case. There was thickening and lamellations of the tubular basement membrane which were seen in the case of a 12-year-old boy as well. Young individuals can also be diagnosed with ADTKD as seen in the present case (30).

Similarly, another case highlights a 41-year-old woman diagnosed with CKD stage 3; she had a previous history of gestational diabetes and hypertension (31). At the time of referral, the patient showed no symptoms, however, had an elevated blood pressure of 154/ 96 mm Hg. Physical examination was unremarkable. The serum creatinine concentration was 1.4 mg/ dL. Her Urinalysis showed bland urine with a random urine albumin-creatinine ratio of 7.6 mg/g. Family history showed a medical history of kidney disease, with her mother suffering from end-stage renal disease (ESRD) and being dependent on hemodialysis for 13 years before succumbing to the disease at the age of 42 years. In the present case, due to uncontrollable hypertension, intravenous nifedipine was started, to control his blood pressure

Kidney biopsy sections subjected to UMOD immunostaining can be informative; but has their limitations that are: the staining cannot be possible in

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most patients, is the operator's skill dependant and requires adequate controls and therefore its value in clinical decision making, is subjected to a critical (32). Research and its application in terms of genetic testing continues to evolve and has opened the possibility to identify the disease of afflicted patients as well as their families. Genetic testing is the gold standard for diagnosis of ADTKD, however, it was not conducted for the patient (33). Pharmacological management of the disease includes treatment with Allopurinol and colchicine. Salt-restricted diet or use of diuretics should be initiated with caution (30).

Individuals requiring renal replacement therapy (RRT), usually lie between the ages of 20-80 years, and show a typically normal urinary sediment, an occasional microhematuria, mild or absent proteinuria (11) and a rare development of secondary focal segmental glomerulosclerosis or glomerulocystic disease (34). The age of onset of kidney failure requiring (RRT) however, varies widely among and within families.

The present study may not be applicable to other geographic regions where the prevalence of ADTKD, and underlying genetic mutations, are not dependent. A thorough assessment including family history, clinical examination, laboratory investigation and genetic testing is necessary to confirm the diagnosis of ADTKD. Future studies should ensure that regular follow-up of the identified cases occurs to understand the disease progression.

Conclusion

Presently, ADTKD has no specific therapies; and recommendations in this setting are based on limited evidence. Its management majorly relies on management of CKD, by following patient care guidelines for the same. Other strategies include Genetic counselling, as the risk of disease transmission to offspring is 50%. It is also noted that the recurrence of ADTKD in cases of renal transplants is not prevalent, hence kidney transplantation currently serves as a safe and most sought-after therapeutic strategy for patients with end-stage kidney disease (ESKD).

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