Uromodulin-related autosomal-dominant tubulointerstitial kidney disease—pathogenetic insights based on a case

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ABSTRACT

Uromodulin-related autosomal-dominant tubulointerstitial kidney disease (ADTKD-UMOD) is a rare monogenic disorder that is characterized by tubulointerstitial fibrosis and progression of kidney function loss, and may progress to end-stage renal disease. It is usually accompanied by hyperuricaemia and gout. Mutations in the uromodulin gene (UMOD) resulting in malfunctioning of UMOD are known to be the cause of ADTKD-UMOD, which is assumed to be an endoplasmatic reticulum (ER) storage disease. As a case vignette, we report a 29-year-old female with a suspicious family history of chronic kidney disease presenting with progressive loss of renal function, hyperuricaemia and frequent urinary tract infections. Urinary tract infections and pyelonephritides may represent a clinical feature of uromodulin malfunction as it plays a protective role against urinary tract infections despite only sporadic data on this topic. ADTKD-UMOD was diagnosed after genetic testing revealing a missense mutation in the UMOD gene. Light microscopy showed excessive tubular interstitial fibrosis and tubular atrophy together with signs of glomerular sclerosis. Electron microscopic findings could identify electron dense storage deposits in the ER of tubular epithelial cells of the thick ascending loop. Immunohistological staining with KDEL (lysine, aspartic acid, glutamic acid, leucine) showed positivity in the tubular cells, which likely represents ER expansion upon accumulation of misfolded UMOD which could trigger the unfolded protein response and ER stress. This review highlights pathophysiological mechanisms that are subject to ADTKD-UMOD.

Keywords: ADTKD-UMOD, hyperuricaemia, tubulointerstitial chronic kidney disease, urinary tract infection, uromodulin

INTRODUCTION

Over many years, non-glomerular autosomal-dominant kidney diseases formed a miscellaneous group of rare inherited disease entities formerly known as medullary cystic kidney disease type 1 and 2, familial juvenile hyperuricaemic nephropathy, and uromodulin/UMOD kidney disease [1]. With progressing research, particularly genetic testing, it became obvious that the majority of these diseases is caused by heterozygous mutations in at least five genes encoding uromodulin (UMOD) [2, 3], hepatocyte nuclear factor-1B (HNF1b) [4], renin (REN) [5], mucin-1 (MUC1) [6], and SEC61A1 [7]. These genetic findings laid the groundwork for a new, gene-based classification of hereditary tubulointerstitial diseases presented by a KDIGO (Kidney Disease: Improving Global Outcomes) consensus conference in 2015, which subsumed these entities under the term autosomal-dominant tubulointerstitial kidney diseases (ADTKD) [8, 9].
therefore, its use is obsolete and no longer recommended.

**CASE VIGNETTE**

A 29-year-old Caucasian female patient has been under nephrological care since 2007 because of relapsing pyelonephritis and progressive chronic kidney disease (CKD). Reduced renal function as well as hyperuricaemia, though without gout, was known at least since the age of 20 when a first renal biopsy was performed. This biopsy showed signs not only of chronic tubular atrophy and interstitial fibrosis of around 25% but also glomerulosclerosis, each of unknown origin. At this time, estimated glomerular filtration rate (eGFR) using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was 58 mL/min/1.73 m² (reference range > 90 mL/min/1.73 m²), serum creatinine 134 μmol/L (reference range 58–96 μmol/L) and proteinuria was <60 mg/L in spot urine (reference range <150 mg/L) and 671 mg per 24 h. Because of persistent hyperuricaemia, the patient underwent genetic testing for Lesch–Nyhan syndrome that turned out negative. Over the years, the patient suffered from relapsing urinary tract infections, flank pain and pyelonephrites, sometimes leading to hospitalization. In most of these cases, urine cultures showed infections with Escherichia coli. In 2016, she presented with an elevated serum creatinine of 198 μmol/L (eGFR using CKD-EPI formula 28.8 mL/min/1.73 m²) and mild hyperuricaemia (451 μmol/L). Urinalysis showed no proteinuria (<60 mg/L). Urinary sediment analysis revealed no erythrocyturia but mild leukocyturia and once more bacteriuria. In renal ultrasound, both kidneys were of normal size (9.6 cm and 10.9 cm in length, respectively) with increased echogenicity of the parenchyma and several simple parapelvic cysts (3–9 mm). The patient had no history of arterial hypertension and did not receive any long-term medication. Due to the progression of kidney disease, we performed a second kidney biopsy. Renal histology showed excessive tubular atrophy and tubulointerstitial fibrosis of 60%. Five out of 13 glomeruli showed global atrophy, tubulointerstitial fibrosis or glomerulosclerosis. However, the remaining glomeruli were without histopathologic alterations. Immunofluorescence for immunoglobulins A, G and complement C3 was negative.

Family history revealed end-stage renal failure of unknown reason in the maternal grandfather and uncle of the patient, both of whom received a kidney transplant. The mother was diagnosed with CKD in 1966. Further information on the patient’s relatives was denied by the patient with respect to privacy protection. Since at least one family member in three successive generations was affected by unclear CKD the pedigree was highly suspicious of an autosomal-dominant inherited disease (Figure 1). Therefore, after genetic counselling, stepwise genetic testing on ADTKD was performed. By this, no mutation of the MUC1 gene was found. However, direct sequencing of the 10 coding exons (exon 2–11) of the UMOD gene via two separate PCR assays showed a heterozygotic mutation in exon 3: a nucleotide exchange at position c.707 of cytosine for guanine (c.707C > G) resulted in an exchange of proline for arginine at position 236 in the protein (p.Pro236Arg). Altogether, the patient was diagnosed with UMOD-related ADTKD (ADTKD-UMOD).

**BIOPSY FINDINGS SPECIFIC FOR ADTKD-UMOD**

Based on the genetic findings, immunohistological staining of uromodulin was performed. While immunohistochemistry in normal, wild-type UMOD cells shows that uromodulin is located mainly at the apical membrane and to a much lower extent at the basolateral membrane of the thick ascending loop (TAL) of Henle [10] (Figure 2A); in our case, staining was positive throughout the cytoplasm and perinuclearly while it was missing at the apical membranes (Figure 2B). Similarly, uromodulin was detected in atrophic and collapsed tubuli. Moreover, electron microscopy showed thickening of tubular basement membranes and vacuolated tubular epithelium as well as extensive electron dense material in the endoplasmatic reticulum (ER), which is likely to represent protein deposits of misfolded uromodulin (Figure 2C). In addition, deposits of granular material were found near the ER, probably representing storage deposits of misfolded uromodulin (Figure 2D). For histological diagnosis or at least special immunohistological staining, it is necessary that clinicians report any suspicion of ADTKD to the nephropathologist as the findings in light microscopy such as tubular atrophy, tubulointerstitial fibrosis or glomerulosclerosis are not different from several other renal diseases.

**ADTKD-UMOD**

ADTKD-UMOD is the most common form of ADTKD with presumably very low overall prevalences. In a nationwide disease registry (UMOD-Related Kidney Disease Registry) of the Wake Forest University School of Medicine, fewer than 2000 families have been identified with this disorder [11]. While there are currently no epidemiologic data on the prevalence of ADTKD-UMOD in Germany, nationwide prevalence in Austria is estimated at 2.12 cases per million population and 0.73 per 1000 patients receiving renal replacement therapy [12, 13]. However, the disease is very likely to be underdiagnosed (see family history in our case vignette). As our case indicates, typical histopathological signs in the renal biopsy are obviously absent. Thus, the number of newly diagnosed ADTKD-UMOD is <1 in 1000 renal biopsy specimens, underlining the need for a close dialogue between nephrologists and pathologists in suspected cases.

Clinical features common to all ADTKD forms include the following: no or mild proteinuria (<1 g/day), bland urinary sediment, normal or slightly decreased kidney size on sonography and no history of severe arterial hypertension. Renal cysts may be reported frequently, but these findings are not constant in all cases of ADTKD and are often missing in early stages of the disease. Therefore, cysts are not a required criterion and previous
FIGURE 2: (A) Immunohistochemical staining with uromodulin in wild-type UMOD regularly shows strong positivity at the apical membrane of tubular epithelial cells of the thick ascending limb of Henle. (B) Immunohistochemical staining with uromodulin in ADTKD-UMOD shows perinuclear positivity in flattened tubular epithelial cells of the thick ascending limb of Henle whereas apical staining is missing. (C, D) Electron microscopy of tubular cells: (C) cytoplasm shows hyperplasia of ER stacks that are filled with fine granular deposits of dense material (arrows) probably representing accumulation of misfolded uromodulin and (D) storage deposits of granular material in hyperplastic ER. (E) Immunohistochemical staining for KDEL sequence (lysine, aspartic acid, glutamic acid and leucine) shows intense positivity in tubular epithelial cells of the TAL, which likely represents ER expansion upon accumulation of misfolded uromodulin which could trigger the unfolded protein response and ER stress.
nomenclature (e.g. medullar cystic kidney disease) might be misleading [14]. In UMOD-ADTKD, hyperuricaemia and gout are characteristic trademarks. The latter is present in 75% of affected men and 50% of affected women, respectively. As our case illustrates, frequent urinary tract infections may represent a clinical feature of uromodulin malfunction in ADTKD-UMOD patients. Data on renal survival suggests a variable decline in renal function with patients reaching end-stage renal disease (ESRD) at an age range from 19 to >70 years [15, 16].

UROMODULIN

Uromodulin, formerly named Tamm–Horsfall protein, is the most abundant glycoprotein in human urine with excretion rates of 50–150 mg daily, and is produced exclusively in tubular epithelia of the TAL of Henle. After synthesis as the precursor protein of 640 amino acids, a signal peptide sequence of 24 N-terminal amino acids for directing the protein into the ER is cleaved. Uromodulin contains high amounts of cysteine residues (48 in total) which are responsible for maintaining correct tertiary folding by building intramolecular disulfide bonds in the oxidative milieu of the ER, three epidermal growth factor domains, one zona pellucida-like domain, and one stretch of hydrophobic amino acids at the C-terminus that serves as transmembrane anchor. After membrane anchoring via a glycosyl phosphatidylinositol anchor at position 614, amino acids 615–640 are cleaved from the C-terminus and seven of eight predicted N-glycosylation sites are glycosylated in the ER [17, 18]. At the apical membrane, uromodulin is cleaved at the C-terminus at position 587 next to a zona pellucida domain. In the urine, uromodulin is found mainly in high-molecular-weight polymers that are mediated by zona pellucida domains [19]. The enzyme responsible for the physiological release of uromodulin in the urine could be identified as hepsin, or TMPRSS1, a member of type II transmembrane serine proteases in 2015 [20].

The role of uromodulin is not yet fully elucidated; however, it has been reported to serve as a multifunctional protein involved in water and electrolyte homeostasis, kidney stone formation, and prevention of urinary tract infections [21]. Studies in knockout mice and in vitro studies could show an inhibitory effect of uromodulin on calcium oxalate and calcium phosphate crystallization due to its sialylated, negatively charged glycans [22]. Umod-knockout mice develop spontaneous kidney calcification and kidney stones that are composed of calcium oxalate and calcium phosphate [23]. Furthermore, uromodulin may prevent urinary tract infections as it is capable of binding type 1-fimbriated E. coli [18, 24]. Umod-knockout mice are more prone to bacterial colonization of the bladder [25]. Raffi et al. reported a high susceptibility to cystidies and pyelonephritides caused by Proteus mirabilis, Klebsiella pneumoniae and Staphylococcus saprophyticus in Umod-knockout mice [26, 27]. In humans, high uromodulin levels in the urine are associated with lower risk for urinary tract infections, which might indicate a protective effect of uromodulin against bacterial infections of the bladder [28]. Uromodulin levels in the urine decrease with loss of eGFR in CKD, which may reflect progressive destruction of tubuloeptithelial cells [29]. Serum levels of uromodulin show a broad variability in CKD. Prajzer et al. [30] reported an overall inverse relationship between eGFR and uromodulin with higher uromodulin serum levels in progressive kidney disease. This could be caused by defective uromodulin secretion and back-leakage of uromodulin from the urine through damaged tubular epithelium. However, the lowest serum and urine levels of uromodulin were measured in patients with lowest eGFR. This seems to be related to advanced tubular damage and decrease of intact tubular cells.

Wolf et al. reported the case of a patient with ADTKD-UMOD and ESRD at the age of 18 years who presented with recurrent urinary tract infections; however, the patient also suffered from vesico-ureteral reflux, which may confound these observations. After reflux surgery, urinary tract infections persisted, which could be a hint to the pathophysiological role of uromodulin for bacterial infections [31]. Likewise, our patient was repeatedly admitted to the hospital because of severe urinary tract infections and pyelonephritis. There have been at least four episodes of pyelonephritides and urinary tract infections from 2007 to 2016, all of which were caused by E. coli except for one single isolation of Staphylococcus lugdunensis in 2015. Because of this, the patient underwent urological diagnostics that could not detect any abnormalities in the urinary tract system. Therefore, frequently recurring infections with E. coli in our patient might be a clinical equivalent to the experimental results reported above.

HYPERURICAEMIA IN ADTKD-UMOD

In humans, the kidney accounts for >70% of overall urate excretion and hyperuricaemia is known to result from reduced renal urate clearance. In the glomerulus, urate is filtered into the primary urine and almost completely reabsorbed, secreted and again reabsorbed in the proximal tubulus (four-component model) [32]. Therefore, hyperuricaemia in UMOD-ADTKD is likely due to increased urate reabsorption. While the exact pathophysiological relations are still not completely understood, several findings and models propose possible mechanisms responsible for hyperuricaemia: uromodulin contributes to water homeostasis and urine concentration. It was shown to regulate the potassium channel ROMK (Renal Outer Medullary Potassium [K] channel), which is essential for salt reabsorption in the renal tubuli, by increasing its membrane expression [33]. Also, it enhances the activity of the Na⁺, K⁺ and 2Cl⁻ cotransporter (NKCC2). This electroneutral transporter serves to reabsorb sodium, potassium and chloride from the primary urine and to preserve the osmotic gradient between renal cortex and medulla. Uromodulin can up-regulate the apical expression of NKCC2 [34]. Thus, decreased levels of uromodulin decrease renal sodium and chloride reabsorption, which leads to a hypovolemic state and may promote proximal reabsorption of urate. Scolari et al. [35] hypothesized an indirect mechanism that reduced sodium uptake in TAL cells is compensated for by enhanced sodium reabsorption in the proximal tubule and consequently enhances the activity of the urate transporter. Additionally, uromodulin forms a gel-like water-impermeable physical barrier in the tubular lumen owing to its hydrophobic properties when assembled in filaments [10]. Lack of intact uromodulin on the luminal surface and thus absence of this physical water permeability barrier increases water influx in the TAL. This would reduce sodium and chloride reabsorption by the TAL NKCC2 cotransporter, enhancing reabsorption of sodium and chloride in the proximal tubule. This process is coupled to and therefore facilitates urate reabsorption in ADTKD-UMOD as hypothesized by Scolari et al. [35]. Liu et al. could show upregulation of two of three urate transporters in the TAL cells. The authors also discuss a two-step event that leads to hyperuricaemia: because of compensatory sodium and chloride reabsorption in the proximal tubule the Na⁺/H⁺ exchange increases the H⁺/urate exchange [36].
In UMOD-related diseases, amino acid changing mutations cause defects in uromodulin maturation and secretion. Abnormal UMOD gene products are shown to accumulate in the ER around the nucleus. It is likely that abnormal uromodulin also alters the function of multiple transporters and channels in the TAL responsible for sodium reabsorption. As already discussed, mild natriuresis is believed to increase reabsorption of uric acid [32, 37]. Moreover, ER stress causes abundant expression of hypoxia-inducible molecules thus leading to mitochondrial dysfunction [38]. This ultimately results in increased apoptosis of TAL cells [39]. Transcriptional profiling studies in mice could show up-regulation of peptides and proteins that are involved in inflammation and fibrosis [40]. Light microscopy of the renal biopsy in our patient showed extensive tubulointerstitial fibrosis and tubular atrophy.

GENETICS AND PATHOPHYSIOLOGY

The UMOD gene is located on chromosome 16 (chr16p12.3); mutations causing ADTKD-UMOD are mostly reported in exons 3 and 4 (~90% of all cases) leading to missense mutations and malfolding of the protein [41]. Most mutations affect a cysteine residue and consequently establishing of disulfide bonds [3, 42]. In 2003, Rampoldi et al. were first to show a delayed intracellular transport of uromodulin and its retention in the ER. Also, uromodulin secretion in the urine is significantly reduced in affected ADTKD-UMOD patients compared with healthy individuals [43]. Although several studies showed impaired secretion of uromodulin in ADTKD-UMOD and thus could replicate the findings of Rampoldi et al. [44, 45], the reason for the intracellular transport defect is still not yet fully elucidated. It is assumed that uromodulin accumulation in tubular cells is due to misfolding of the protein, causing the unfolded protein response of the ER and subsequently ER stress. If degrading of misfolded proteins cannot be achieved within a certain time span, apoptosis is initiated [35]. Key molecules in pathways involved in ER stress and apoptosis associated with the unfolded protein response are Ire1 [46, 47], ATF6 [48] and PERK [49]. Thus, ADTKD-UMOD is considered a storage disease. However, in some ADTKD-UMOD mutations, normal basolateral trafficking and excretion of uromodulin on the basolateral membrane of TAL cells was reported in vitro. Concordantly, some ADTKD-UMOD patients showed higher serum levels of uromodulin. The authors speculate that basolateral secretion of misfolded UMOD in the tubulointerstitial space could initiate an inflammatory response, further promoting tubulointerstitial fibrosis [50].

In our patient, by immunohistological staining loss of apical staining and thus diffuse accumulation of uromodulin in the cytoplasm of TAL cells could be shown (Figure 2A and B). In electron microscopy, electron dense material in hyperplastic ER around the nucleus of TAL cells could be shown (Figure 2A and B). In some ADTKD-UMOD patients described in 31 peer-reviewed publications and 202 patients described in 31 peer-reviewed publications and review articles, normal basolateral staining was found in tubular epithelial cells of the TAL throughout the cytoplasm (Figure 2E).

In ADTKD-UMOD, the current c.707C>G, p.Pro236Arg mutation has been previously described and was shown to result in defective transport of the misfolded protein from the ER to the Golgi apparatus [11, 56]. In the reported patient, according to 9 out of 10 bioinformatical prediction programmes, the reported missense mutation leads to misfolding of the coded protein uromodulin and its retention in the ER, which can be demonstrated by electron microscopic and immunohistochemical findings presented above (Figure 2C–E). Until now, this mutation was reported to be associated with smaller caliber renal arteries, which could also be correlated with uric acid serum levels and reduced GFR. However, this finding was not present in children affected with the mutation and could thus be the result of so far unknown underlying mechanisms that lead to thickening of vessel walls and consequently smaller diameters of vessel lumina [57].

MANAGEMENT

Prevalence of ADTKD may be higher than previously thought due to a high rate of current underdiagnosis. Genetic testing for ADTKD is recommended when there is a family history compatible with autosomal-dominant inheritance of unclear CKD, characteristic clinical findings [e.g. bland urinary sediment, absence of proteinuria, hyperuricaemia (ADTKD-UMOD), anaemia during childhood (ADTKD-REN), MODY (HNF1B)] and/or compatible histology of tubular atrophy and interstitial fibrosis in kidney biopsy [9]. If ADTKD-UMOD is confirmed by genetic testing, clinical management also involves screening of family members for possible affection. This is not only to identify affected individuals and to be able to monitor and prevent progressive kidney function loss, but also to identify healthy family members willing to serve as kidney transplant donors. Genetic counselling is recommended for affected individuals and their relatives; before family planning, patients should be informed that 50% of their offspring will inherit the disease. Predictions on renal survival in ADTKD-UMOD patients cannot be estimated precisely as of today. Bollée et al. reviewed the decline of renal function in 107 patients with UMOD mutation. ESRD was observed from the age of 25 to >70 years. Data suggest that UMOD mutations that lead to cysteine substitutions and thus affect intramolecular disulfide bonds and tertiary protein folding might be associated with a lower renal survival than UMOD mutations within polar amino acids [3]. Intrafamilial variability in the age of ESRD onset showed a wide range in patients belonging to the same family with assumably the same UMOD mutation [3]. Moskowitz et al. also reviewed renal survival in 202 patients described in 31 peer-reviewed publications and reported an earlier onset of ESRD and gout in men than in women affected by ADTKD-UMOD. Also, renal survival was lower in mutations within the epidermal growth factor domains.
2 and 3 (mean age at ESRD onset: 45–52 years) compared with the cysteine-rich domains (mean age at ESRD onset: 60–65 years) [42]. Thus, there seems to be a vague correlation between genotype and phenotype (i.e. the decline in renal function) in ADTKD-UMOD and family history serves little to predict eGFR loss. Likewise, the family history of our patient also showed high variability in the progression of CKD and reaching ESRD. As the mutation of our patient is located within the cysteine-rich domains, ESRD statistically may occur around the sixth decade; however, as a female individual, renal survival of the patient could be slightly higher. There are no other epidemiologic data available for the c.707C > G mutation described above.

In ADTKD-UMOD patients, annual testing of kidney function is recommended; also, testing on hyperuricaemia should be considered as it precedes renal function loss. Renal ultrasound can detect cysts, renal calcifications or kidney stones. Also, as was the case in our patient, there may be a history of recurrent urinary tract infections and bacterial colonization with *E. coli*. For affected individuals, there is unfortunately no causal treatment of ADTKD-UMOD. Although there is no specific evidence for the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, these agents can be considered to attend hypertension, which is known to aggravate chronic kidney failure. Losartan should be preferred as it increases excretion of uric acid [59]. If history of gout is present, treatment with xanthin oxidase inhibitors is recommended. While data may suggest that urate-lowering therapy can prevent progression of CKD of other origin [50], this might not be the case in ADTKD-UMOD [60]. Yet, we recommend urate-lowering therapy to prevent gout in ADTKD-UMOD, and because treatment of asymptomatic hyperuricaemia with allopurinol also reduces the risk of cardiovascular events [61] and insulin resistance [62]. Llabiola et al. reported an exaggerated response to furosemide in a patient with ADTKD-UMOD with increased diuresis and sodium excretion. As it is hypothesized that sodium loss and hypovolemia may lead to additional urate reabsorption, loop diuretics should be used with great caution in ADTKD-UMOD patients [63]. ESRD owing to ADTKD-UMOD can be cured by kidney transplantation as it is not reported to reoccur in the graft [64]. In the present family, kidney transplantation was performed on two of the affected family members.

CONCLUSIONS

In conclusion, ADTKD-UMOD is a highly underdiagnosed and thus underreported disease, although it often presents with a suspicious family history of CKD but also distinct clinical features like hyperuricaemia, progressive loss of renal function and probably frequent urinary tract infections as reported above. These findings may raise the suspicion of the disease so that correct diagnosis can be obtained via genetic testing. Histological diagnosis of the disease is limited. In the case of histological confirmation of the diagnosis, special immunostaining and electron microscopy is necessary and requires close communication between the clinician and the nephropathologist.

By instructive electron-microscopic findings in tubular epithelial cells quite compatible with accumulation of misfolded uromodulin in the ER, we report pathogenetic insights into this disease entity based on a case of UMOD-related ADTKD caused by a mutation in exon 3 of the UMOD gene (c.707C > G, p.Pro236Arg). Furthermore, KDEL signal increase in tubular epithelial cells of the TAL is shown, which could be interpreted as an indicator of ER stress and/or ER expansion, which constitutes the pathophysiological groundwork of the ER storage disease.

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Informed consent has been obtained from the patient.

CONFLICT OF INTEREST STATEMENT

The authors declare that the results presented in this paper have not been published previously in whole or part, except in abstract format. J.R., H.-J.G., G.W. and M.B. have nothing to disclose.

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