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Autosomal dominant tubulointerstitial kidney disease: Diagnostic challenges in the absence of genetic testing. A case report

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Abstract. Autosomal dominant tubulointerstitial kidney disease (ADTKD) is a group of rare uncommon genetic disorders characterized by tubular damage and interstitial fibrosis in the absence of glomerular lesions. It has autosomal dominant inheritance and inevitable progression to end-stage kidney disease (ESKD). In nephrological practice, we usually face glomerular diseases that have well-recognized symptoms. Therefore, when we see a patient with impaired kidney function but without any signs of glomerular disease, it is always more challenging to discover the reason for it. The present case illustrates tubulointerstitial lesions due to possible genetic reasons. A 38-year-old non-hypertensive female presented with impaired renal function, a family history of CKD, proteinuria 0,5 g/day, and urinary sediment unremarkable. Relying on her family history, the middle age of onset, the progression to the end-stage kidney disease, and laboratory and histological results, an autosomal dominant tubulointerstitial kidney disease was suspected. Initially, diagnosed tubulointerstitial kidney disease is likely to be secondary to a mutation in genes encoding mucin-1. Pathology findings in this case played a pivotal role in establishing the diagnosis. However, it still needs to be proven by genetic tests. The purpose of this manuscript was to summarize the case of ADTKD, discuss the challenges in diagnosing ADTKD without genetic testing, and emphasize the importance of genetic testing in confirming the diagnosis.

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Аутосомно-домінантне тубулоінтерстиційне захворювання нирок: складність діагностики без генетичного тестування. Клінічний випадок

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Резюме. Аутосомно-домінантне тубулоінтерстиційне захворювання нирок (АДТЗН) – це група рідкісних генетичних порушень, що характеризуються ураженням тубулярного апарату нирок з розвитком інтерстиційного фіброзу за відсутності клубочкових порушень. Успадковується за аутосомно-домінантним типом та характеризується незворотнім прогресуванням до хронічної хвороби нирок 5 ст (ХХН 5 ст). В практичній діяльності нефрологи переважно мають справу із патологією нирок гломерулярної природи із загальновідомими проявами. У випадку виявлення хвороби з порушенням функції нирок, без ознак, які б вказували на ураження гломерулярного апарату, інколи складно встановити причину патології. Представлено наступний клінічний випадок: жінка 38 років з порушеною функцією нирок, без гіпертензії, із сімейним анамнезом щодо захворювання нирок, з протеїнурією 0,5 г/добу та відсутністю інших змін в сечовому осаді. Врахування сімейного характеру захворювання, виникнення його в середньому віці, швидке прогресування до хронічної хвороби нирок 5 ст., даних лабораторних та гістологічних методів обстеження, дозволило припустити АДТЗН, яке може бути пов'язане з мутацією гена, що кодує уромодулін, зокрема муцин-1. Ключову роль у діагностиці даного випадку зіграли результати пункційної біопсії нирки, проте залишається необхідність підтвердження її генетичними тестами.

Ключові слова. ХХН, аутосомно-домінантне тубулоінтерстиційне захворювання нирок, генетичні порушення, муцин-1, уромодулін

Introduction. Autosomal dominant tubulointerstitial kidney disease (ADTKD) is a group of rare uncommon genetic disorders characterized by tubular damage and interstitial fibrosis in the absence of glomerular lesions [1]. It has an autosomal dominant inheritance and inevitable progression to end-stage kidney disease (ESKD). ADTKD is characterized by slowly progressive kidney disease with impaired renal function typi-

cally appearing in the teenage years, and ESKD onset between 40 and 60 years, although this may depend on other variables such as degree of penetrance of the mutation, hyperuricemia, and other comorbidities [1-3].

Four main genetic lesions lead to ADTKD, that encloses mutations in the genes encoding uromodulin (UMOD), hepatocyte nuclear factor 1- β (HNF 1B), renin (REN), and mucin-1 (MUC-1) (Table 1) [1, 4].

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Table 1

Types of autosomal dominant tubulointerstitial kidney disease (medullary cystic kidney disease) [4]

Characteristic	ADTKD due to UMOD mutations (ADTKD-UMOD)	ADTKD due to REN mutations (ADTKD-MOD)	ADTKD due to MUC1 mutations (ADTKD-MUC1)
Inheritance	Autosomal dominant	Autosomal dominant	Autosomal dominant
Urinalysis results	Bland without protein	Bland without protein	Bland without protein
Renal ultrasound	Normal or small kidneys, occasional cysts	Normal or small kidneys, occasional cysts	Normal or small kidneys, occasional cysts
Age of ESRD (years)	20 to 70	40 to 80	20 to 80
Kidney biopsy	Interstitial fibrosis, nondiagnostic	Interstitial fibrosis, nondiagnostic	Interstitial fibrosis, nondiagnostic
Definitive diagnosis	Genetic analysis	Genetic analysis	Genetic analysis
Associated findings	Many family members with gout, some in their teenage years	Low or low-normal blood pressure, hyperuricemia, anemia in childhood, mild hyperkalemia	No associated findings
Treatment	No specific treatment; allopurinol for gout	High-sodium diet or fludrocortisone	No specific treatment
Frequency	Rare	Very rare	Rare
Other names	Uromodulin kidney disease (UKD), medullary cystic kidney disease type 2 (MCKD2), familial juvenile hyperuricemic nephropathy (FJHN)	Familial juvenile hyperuricemic nephropathy type 2 (FJHN2)	Mucin-1 kidney disease (MKD), medullary cystic kidney disease type 1 (MCKD1)

Abbreviations: ADTKD, autosomal dominant tubulointerstitial kidney disease; ESKD, end-stage kidney disease; REN, renin gene mutation; MUC1, mucin -1 gene mutation; UMOD, uromodulin gene mutation.

This classification is more practical as it is based on a certain genetic mutation, not on diagnostic criteria as it was before. Most clinical, diagnostic, and histologic findings are not remarkable in every genetic type. In the KDIGO guidelines, it is noted that there is usually the presence of a family history of kidney disease, and members of the family are unaware of it and therefore not diagnosed appropriately until the end stage of CKD or even death.

We, nephrologists, get used to the fact that glomerular diseases are usually one of the most common causes of chronic kidney disease (CKD) in adults. Therefore, when we see a patient with impaired kidney

function but without any signs of glomerular disease it is always more challenging to discover the reason for it, especially without access to appropriate genetic testing. The present case illustrates an adult case of tubulointerstitial lesions due to a possible genetic reason. The purpose of this manuscript was to summarize the case of ADTKD, discuss the challenges in diagnosing ADTKD without genetic testing, and emphasize the importance of genetic testing in confirming the diagnosis.

Case report. A 38-year-old female was referred to the SI "Institute of Nephrology NAMS of Ukraine" due to probable CKD, discovered during a routine GP check-up. She presented asymptomatic. There was

no history of hypertension, smoking, alcohol intake, chemical or drug exposure, allergies, or any additional medical conditions. Her physical examination was unremarkable. She reported a family history of CKD. Her sibling's brother had impaired renal function, and her father died at the age of 48 due to CKD being on a PD. Blood tests were as follows: hematocrit 32,3%; hemoglobin 11.7 g/dL; uric acid – 430,4 mmol/l urea 10,04 mmol/L (normal value 2,5-8,3 mmol/L); serum creatinine 143,1 μmol/L; GFR-Epi 40 ml/min; total protein – 81,1 g/l; albumin- 45,7; total cholesterol – 5,87 mmol/l; proteinuria 0,5 g/day; urine pH – 6, urinary

density – 1018. Urinary sediment was unremarkable. HIV, HCV, HBV, and RW were negative. ANA, p-ANCA, c-ANCA, and anti-glomerular basement membrane antibodies, were negative according to medical records. A renal sonogram disclosed two kidneys, normal in shape and size, without any abnormalities. A kidney biopsy was performed. Light microscopy of the paraffin and semithin sections showed cores of renal cortical-medullary tissue including a total of 16 glomeruli, ten of which were globally sclerosed, 1 – with thickening and splitting of the glomerular capsule, other glomeruli were unremarkable or slightly enlarged (Fig. 1).

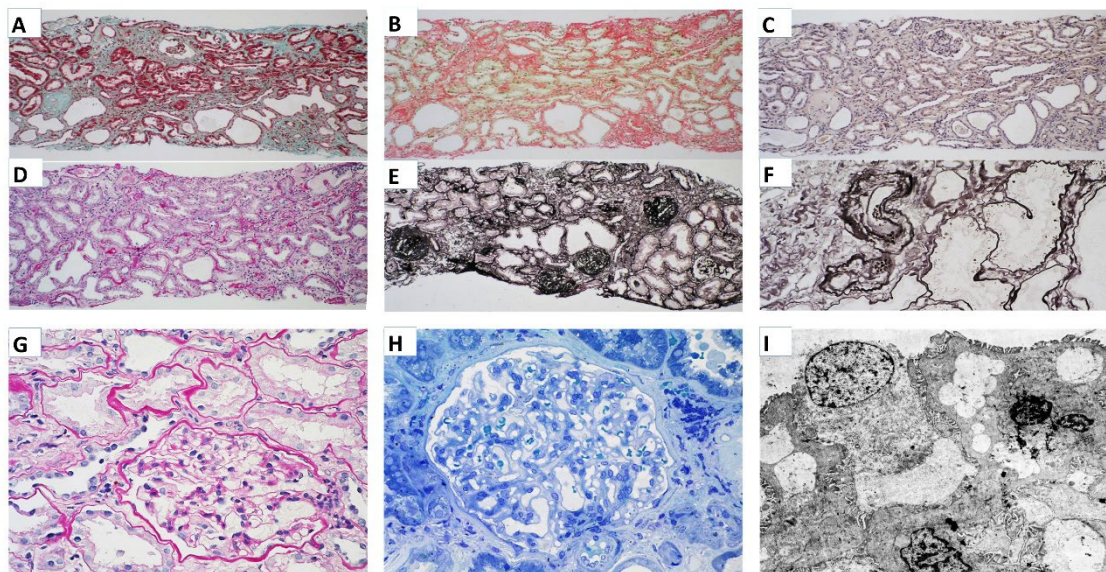


Fig. 1. The chronic tubulointerstitial kidney disease with 58% (14/24) glomerulosclerosis and unremarkable other glomeruli.

A – Masson-Goldner stain, x100. B – Picro-Sirius, x100. C – Congo Red, x100. D – PAS, x100. E – PAMS, x100. F – PAMS, x400 G – PAS, x400, H – Semithin section, methylene blue, x400. I – Transmission electron micrograph of the relatively normal glomerulus, original magnification x2400

Frequent tubular dilatation of distal convoluted tubule. Tubular atrophy was 30% and interstitial fibrosis was 50%. Blood vessels showed mild intimal sclerosis in the interlobular artery. Immunofluorescence of the frozen sections with antibodies to IgG, IgA, IgM, and C1q, negative. Electron microscopy: glomerulus with global sclerosis, others – without mesangial widening, thickening of the basal membrane and electron-dense deposits, podocyte foot processes without effacement. In the epithelial cells of the proximal and distal convoluted tubules were numerous mitochondria and light vacuoles. Intranuclear inclusions were not present. Thickening of the tubular basement membrane of a few tubules was discovered. The pathology report was as follows: tubulointerstitial nephritis, NOS most probable due to genetic mutation of mucin-1 connected kidney disease. The patient has commenced on enalapril 5 mg twice a day and an appropriate diet. She was recommended a genetic test but due to the impossibility of performing it in Ukraine at that time, she refused it. She also decided not to childbirth.

Discussion. Differentiating ADTKD from other kidney disorders depends upon the clinical presenta-

tion. Urinalysis can help to distinguish ADTKD from other causes of CKD, both genetic and acquired, which often affect the glomerulus (such as congenital focal segmental glomerulosclerosis, Alport syndrome, post-streptococcal glomerulonephritis, and immunoglobulin A nephropathy). The main feature of the mentioned disorders is blood and/or protein in the urine, whereas patients with ADTKD have a bland urinary sediment that we also observed in our patient that's why we didn't take them into account. In young individuals presenting with gout, the differential diagnosis includes other potential causes of early-onset hyperuricemia, such as hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency (Lesch-Nyhan) syndrome, kidney disease known to be caused by a different disorder, or the use of thiazide diuretics. These diagnoses are usually obvious from the clinical evaluation. As our patient has not had any signs of elevated uric acid we excluded these disorders.

Our patient presented with a family history of undiagnosed CKD while her father progressed to end-stage kidney disease. As on admission, an elevation of serum creatinine was discovered without severe daily protein-

uria, the kidney biopsy was considered mandatory. In addition, the family background showed a progressive trend to the end-stage kidney disease that urged to obtain tissue samples immediately, even though at advanced stages of CKD benefits from kidney biopsy with diagnostic purposes appear to be lower. In our opinion, a primary glomerulopathy should not be the reason for impaired kidney function in this case due to the absence of long-term, severe proteinuria and hypertension. The pathology report proved our thoughts revealing interstitial kidney disease without any other signs. This fact has led us to the thought of some genetic disorders.

Relying on her family history an autosomal dominant pattern of inheritance could be suspected. The middle age of the adult onset of the disease and the progression to the end-stage kidney disease was also a good point to take into consideration. It should be noted, that the patient was not hypertensive either at the time of the first presentation or the stage 3 CKD. In view of the above findings, an autosomal dominant tubulointerstitial kidney disease was taken into consideration [1-3].

The most remarkable diagnostic features of the main four types of ADTKD are as follows. ADTKD-UMOD is characterized by the presence of hyperuricemia and gout in adults, cysts usually are rare and, if present are likely cortical [1, 5, 6]. As hyperuricemia and gout are common clinical features among ADTKD with the mentioned mutation further management depends upon whether or not the patient has an established diagnosis of gout. Because patients with ADTKD-UMOD and established gout have genetically determined gout and are at high risk for future gout flares and tophus development, they qualify for pharmacologic urate-lowering therapy. The selection, initiation, and duration of pharmacologic urate-lowering therapy are similar to that for the general population. For patients with ADTKD-UMOD who have not yet developed gout, the pharmacologic urate-lowering therapy is not recommended. However, some experts may offer urate-lowering therapy to patients who have marked hyperuricemia (>9 mg/dL [>535 micromol/L]) or a strong family history of early-onset gout, although there are no data to support this approach [5]. There is no high-quality evidence that urate-lowering therapy with allopurinol or febuxostat slows the rate of progression of CKD in patients with ADTKD-UMOD, although some observational studies have suggested a possible benefit with allopurinol [7-10]. ADTKD-REN pathogenic variants are the least common cause of ADTKD, but they are most distinctive. Low or normal blood pressure, hyperuricemia, mild hyperkalemia, and anemia in childhood (usually resolves in puberty) are present. Patients with this genetic variant develop gout in their late teens. Specific treatment options are available only for this subtype and include a high-sodium diet or fludrocortisone [5, 11]. In ADTKD-HNF1B maturity onset of diabetes mellitus, pancreatic atrophy, and cystic kidneys are presently combined with hypomagnesemia, hypokalemia and asymptomatic elevation of

liver function tests [12]. Ultimately, ADTKD- MUC-1 results in abnormal mucin-1 protein production, which accumulates intracellularly in the loop of Henle, distal tubule and collective duct resulting in tubular atrophy and glomerulosclerosis [5, 13], which are present in our patient according to the pathology report. The primary manifestation of ADTKD-MUC-1 is an unexplained progressive CKD or reduced eGFR revealed during routine laboratory testing as well as relatively bland, without hematuria or significant proteinuria urinalysis. Some patients develop hyperuricemia and gout, but unlike other variants of ADTKD gout is a late manifestation and usually correlates to the degree of kidney dysfunction [14]. All mentioned findings can also be observed in our case. A kidney ultrasound usually reveals normal kidneys, rarely medullary cysts which are common but not diagnostic in patients with this genetic type [14].

Mucins are known as high molecular weight heavily glycosylated transmembrane proteins. They could be either secretory or membrane-bound. MUC1 is a membrane-bound mucin that is highly expressed throughout the distal nephron and is involved in the protection and lubrication of the distal tubular lumen [15]. As a transmembrane protein, it plays a significant role in plenty of intracellular functions, particularly in signal transduction [15].

In patients suspected of having ADTKD, the diagnosis can be confirmed with genetic testing. Genetic testing is preferable to kidney biopsy in this setting. However, genetic testing can be expensive. Thus, it may be preferable to test a family member who is affected (based on clinical features) and who has sufficient financial resources or insurance for the test. Although genetic testing for UMOD, REN, and HNF1B mutations is well-established in many European countries, MUC1 genetic testing remains challenging even there [16]. The optimal approach to genetic testing for ADTKD is to perform whole exome sequencing (WES) or to order a kidney disease gene panel. However, WES and existing gene panels are inadequate for the diagnosis of ADTKD-MUC1 since these methods identify only approximately 1 percent of the pathogenic variants that cause ADTKD-MUC1 [17, 18]. A clinically approved (Clinical Laboratory Improvement Amendments [CLIA]-approved) genetic test for MUC1 is available from the Broad Institute of Harvard Medical School and the Massachusetts Institute of Technology. This test only identifies the cytosine duplication, the most common pathogenic variant in ADTKD-MUC1. There are also centers available in Europe that provide similar MUC1 genetic testing [19].

Unfortunately in Ukraine, such kind of genetic testing has not been available till now, possibly due to its cost. For Ukrainian patients with suspicion of ADTKD, it is quite expensive to visit other European countries and overcome genetic testing. In addition, it is difficult to persuade patients that genetic testing is essential due to the fact that confirmation of the diagnosis will not

lead to the initiation of specific therapy for this disease, because it does not currently exist.

Treatment usually consists primarily of supportive care including blood pressure control and management of the complications of CKD (such as anemia, metabolic bone disease, metabolic acidosis, and electrolyte abnormalities) for all patients as well as additional measures that are specific to certain types of ADTKD. There are some specific considerations in the management of CKD among patients with ADTKD. Most patients with ADTKD are normotensive and do not have substantial proteinuria. As a result, they are less likely to be treated with angiotensin inhibitors, which as we know can slow the progression of proteinuric CKD. In patients who are hypertensive and have hyperuricemia, losartan would be a preferable treatment, as it has been shown to increase urinary uric acid excretion [20, 21]. There is no evidence that angiotensin inhibitors slow the progression of CKD in patients with ADTKD.

In ADTKD, diuretics should be used with caution or avoided, as they may aggravate hyperuricemia

and volume depletion [22]. In order to compensate for probable urinary concentration defects abundant water intake is recommended. Nonsteroidal anti-inflammatory drugs as well as nephrotoxic antibiotics should be avoided [1].

Conclusion. In conclusion, initially diagnosed tubulointerstitial kidney disease is likely to be secondary to a mutation in genes encoding mucin-1. Pathology findings in this case played a pivotal role in establishing the diagnosis. However, it still needs to be proved by genetic tests.

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The authors' contribution.

Liudmyla Surzhko: Conception and design, preparation of the manuscript;

Valentyn Nepomnyashchy: Morphology, final editing.

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