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Alicia López-Abad[a,*], Santiago Llorente Viñas[b], Pedro López Cubillana[a], Santiago Llorente Esteban[c], Laura Aznar Martínez[a], Natalia Vidal Crespo[a], Guillermo Antonio Gómez Gómez[a], Juan Bernardo Cabezuelo Romero[b]

[a] *Servicio de Urología, Hospital Clínico Universitario Virgen de la Arrixaca, El Palmar, Murcia, Spain*

[b] *Servicio de Nefrología, Hospital Clínico Universitario Virgen de la Arrixaca, El Palmar, Murcia, Spain*

[c] *Graduado en Farmacia, Spain*

[*] *Corresponding author.*
E-mail address: alicialopezabad@gmail.com (A. López-Abad).

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Eliminating the concept of unknown chronic kidney disease: 2 cases of autosomal dominant tubulointerstitial nephropathy with pathogenic variant *MUC-1*

Eliminando el concepto de enfermedad renal crónica no filiada: a propósito de 2 casos de nefropatía túbulo-intersticial autosómica dominante con variante patogénica *MUC-1*

Dear Editor,

Confirming a diagnosis for certain renal diseases is only possible with a genetic study. This is the case for autosomal dominant tubulointerstitial kidney disease (ADTKD), as defined by the KDIGO guidelines in 2015.[1]

ADTKDs manifest as progressive loss of renal function, with negative or anodyne proteinuria and usually with normal urinary sediment. On ultrasound, the kidneys are normal or small size, with inconsistent presence of corticomedullary cysts. Renal biopsy is nonspecific, showing only evidence of interstitial fibrosis and tubular atrophy. The five most frequent known causative genes are: *UMOD, MUC-1, REN, HNF1B* and *SEC61A1*, with differential clinical characteristics among them (Table 1).[2–5] Penetrance is close to 100% and there may be intra- and interfamilial variability. They constitute the third most common group of monogenic renal disease, after autosomal dominant polycystic kidney disease and type IV collagen disease.[4]

We present 2 cases diagnosed in our center.

The first case is a 23-year-old female patient, with no relevant medical history, who was consulted for renal function deterioration with creatinine of 1.4 mg/dl, CKDEPI 53 ml/min/1.73 m^2, urine albumin/creatinine ratio of 7.4 mg/g and no alterations in urinary sediment. On ultrasound, the kidneys were of normal size and morphology, although slightly hyperechogenic, with no evidence of renal cysts. There was nothing remarkable in the anamnesis: she had no history of urinary tract infections or nephritic colic, no nephrotoxic intake and no cardiovascular risk factors (she had blood pressure of 120/70 mmHg). Regarding family history (Fig. 1): her maternal great-grandmother died at 35 years of age of "nephropathy," her maternal grandmother started dialysis at 45 years of age, her maternal aunt started dialysis at 55 years of age and her mother started dialysis at 48 years of age. In all 3 cases, chronic kidney disease (CKD) was not affiliated and had been related to vascular profile because she had arterial hypertension at 35–40 years of age. We performed more studies (ANA, anti-DNA, ANCA, ENA, C3/C4, IgA/M/G, proteinogram, HIV/HBV/HCV): all were negative or normal. The patient presented progressive deterioration of renal function with no other potential causes. She refused renal biopsy. Given the familial autosomal dominant profile, clinicians requested a genetic study, which detected a pathogenic variant in the *MUC-1* gene, causing NTIAD. The patient is now 28 years old, with advanced chronic kidney disease (creatinine 5.2 mg/dl CKDEPI 10 ml/min/1.73 m^2), so the progression has been faster than in her other relatives.

The second case is a 29-year-old male, with medical history of arterial hypertension of one year with good control with low-dose antihypertensive drugs; he also had meningitis (2015) and previous appendectomy. He was referred to us because of renal function deterioration (creatinine 2 mg/dl, CKDEPI 38 ml/min/1.73 m^2), with an urine albumin/creatinine

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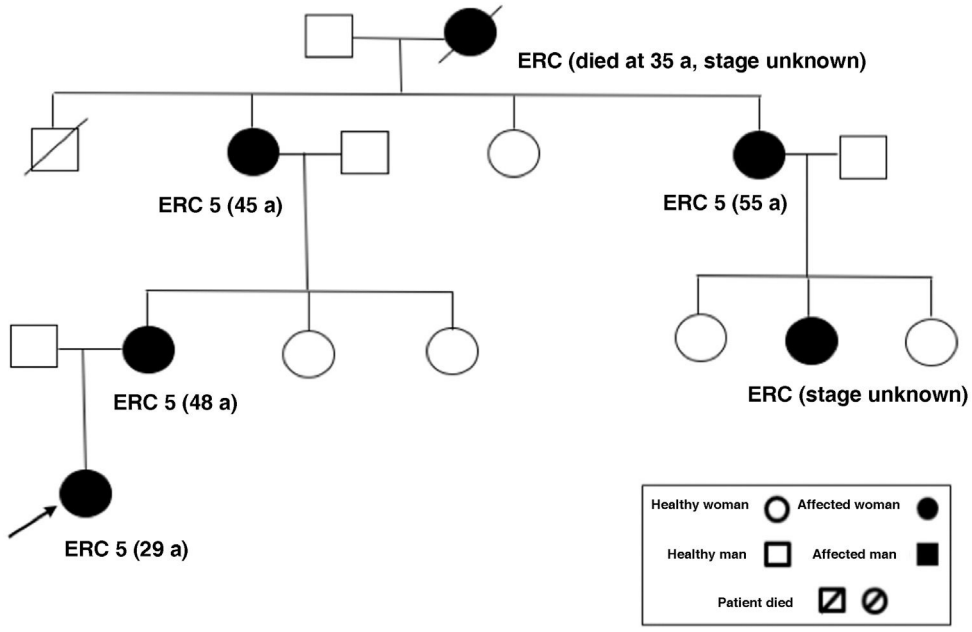

Fig. 1 – Family tree.

Table 1 – Characteristics of the different NTIADs.

Causal gene	Features
REN	Early onset anemia, disproportionate to the degree of renal failure Hyperkalemia and hyperuricemia Normal or low blood pressure
HNF1B	Hypomagnesemia, hyperuricemia, alteration of liver function tests Presence of cortical and bilateral renal cysts, renal hypoplasia, glomerulocystic disease, renal agenesis, renal hyperechogenicity in fetal and neonatal period MODY5 diabetes, genital malformations and pancreatic atrophy
MUC-1	No characteristic features other than tubulointerstitial fibrosis Cortico-medullary cysts may be present
UMOD	Inappropriate decrease in the fractional excretion of uric acid Early hyperuricemia (before the onset of renal insufficiency) Defect in the urinary concentration capacity Decreased urinary excretion of uromodulin Cortico-medullary cysts may be present
SEC61A1	Congenital anemia, leukopenia, and neutropenia Delayed growth Uvula bifida, abscess formation, cleft lip

ratio of 290 mg/g, with no alterations in urinary sediment. We had no previous lab analyses or reports (he used to live in another city). Ultrasound revealed the kidneys measured 10 cm and presented poor corticomedullary differentiation and small bilateral cortical cysts. As for family history: his paternal grandfather started dialysis at age 73 (no reports were available, he resided in another city and he was deceased), parents had no history of renal disease and no other known nephrological history in his family. There was no deafness in the family. We performed an extensive study (ANA, anti-DNA, ANCA, ENA, C3/C4, cryoglobulins, IgA/M/G/IgG4, proteinogram, HIV/HBV/HCV): everything was negative or normal. A Fabry screening study (α-galactosidase levels) was also negative. We did not consider performing a renal biopsy due to the important chronicity data in the ultrasound. In view of the non-filial CKD, the patient's age and the family history, we decided to request a genetic study, which detected a pathogenic variant in the *MUC-1* gene, that was the cause of autosomal dominant interstitial nephropathy.

In conclusion, NTIAD should be suspected in young patients with non-infiltrative CKD without glomerulonephritis data and with a family history of nephropathy, whose reliable diagnosis is only possible with a genetic study.[6,7] Thanks to technological advances in genetic studies in recent years, there are now affordable and efficient tests for well-selected patients.[8,9]

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Verónica Andreina Barcia Odor*, Elena Monfá, Benjamin de León, Catherine Martinez-Rosero, Silvia Sanchez-Montero, Carmen Barnes, Cristina Lucas, Arancha Sastre, Jorge Estifan, Mario Prieto

Servicio de Nefrología, Complejo Asistencial Universitario de León, León, Spain

* *Corresponding author.*
E-mail address: veronicaabarcia@gmail.com (V.A. Barcia Odor).

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A rare case of two successful pregnancies in a female patient on hemodialysis

Un caso raro de dos embarazos exitosos en una paciente en hemodiálisis

Dear Editor,

The occurrence of pregnancy in women with Chronic Kidney Disease (CKD) is unusual and these women are prone to more complications, especially among those on dialysis. Nevertheless, the high rate of complications such as hypertension, polyhydramnios, pre-eclampsia, restricted intrauterine growth and preterm birth make this physiological state a challenge in women with advanced CKD.

We report a case of a 29-year-old female patient with an obstetric history of a fetal loss at 31 weeks of gestation at the age of 18, in the sequence of an unsupervised pregnancy, diagnosed with gestational hypertension and severe pre-eclampsia at the time of delivery. At the age of 20, she presented with hypertension associated with thrombotic microangiopathy which required hemodialysis initiation. She was followed up as an outpatient in our hemodialysis department with dialysis prescription described in Table 1. Additional medical history of anemia and mineral bone disease associated with CKD controlled with darbopoetin, intravenous iron and vitamin D analogs.

Five months after starting hemodialysis, she was found to be pregnant on a routine abdominal ultrasound, with an estimated gestational age of 12 weeks. At the time, she was passing 1000 mL of urine a day and had a dry-weight of 42 kg. Immediately, dialysis prescription was changed to a 20 hours a week, as shown in Table 1. Pre-dialysis urea values were kept under 60 mg/dL, potassium levels between 4.2 and 5.3 mg/dL, blood pressure maintained under 140/90 mmHg and dry weight was gradually incremented. An increment of dialysis time was proposed to the patient, but she promptly refused. Prenatal care and follow-up were carried out at the Obstetric Unit, with frequent ultrasound checks excluded fetal malformations. At 36 weeks of gestation she was submitted to a programmed cesarean section for pelvic presentation with active contractility. The newborn had a birthweight of 2375 g an Apgar score of 9 at 0′ and 10 at 5′ and normal neonatal development.

After delivery patient returned to similar dialysis prescription (Table 1). Also, she always refused a kidney transplant and there was suspicion of poor therapeutic adherence. Nine years later, she presented with amenorrhea for three consecutive months, and pregnancy was confirmed after the detection of beta-subunit of human chorionic gonadotropin (11568 mUI/mL). Fetal ultrasound showed an embryo with an estimated gestational age of 4/5 weeks. At the time, she was passing 500 mL of urine a day and had a dry weight of 57.5 kg. This time, the total weekly dialysis time was increased to 24 h per week (Table 1). Pre-dialysis urea values were kept under 30 mg/dL. Blood pressure was difficult to control and

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