Mild chronic renal failure with a family history of kidney disease

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The case

A 31-year-old woman (Figure 1: III-1) was evaluated for mild renal failure. The serum creatinine was 1.5 mg/dL and the creatinine clearance 55 mL/min (Cockcroft formula). The blood urea nitrogen and urate levels were 52 and 4.8 mg/dL, respectively. There was a mild microalbuminuria (57 mg/24 h); urinalysis was unremarkable. Renal ultrasonography showed a right kidney of 9.5 cm and a left kidney of 9.2 cm, with normal echogenicity and no cysts; Doppler examination was normal.

The patient’s father (II-2) had a 20-year history of slowly progressive renal failure of unknown origin, leading to dialysis initiation at age 58. A CT scan revealed the existence of small kidneys with several cysts. One month before starting dialysis, he underwent unilateral nephrectomy for renal cell carcinoma. He had suffered a few attacks of gout starting at age 55. The father has one brother (II-4), apparently healthy. The paternal grandfather of the proband (I-1) died at age 60 of uraemia, after a history of gout and heart disease.

Question

What is your clinical diagnosis? What genetic abnormality do you suspect?

Answer

The diagnosis is chronic interstitial nephritis caused by a mutation in the UMOD gene.

Discussion

Based on urinalysis, the mild chronic renal failure in this young patient was most likely attributed to a chronic interstitial nephritis. The family history was highly suggestive of a hereditary disorder, with a male-to-male transmission testifying to an autosomal-dominant trait (Figure 1). The history of gout in both father and grandfather, though of late occurrence, was compatible with a diagnosis of familial juvenile hyperuricaemic nephropathy (FJHN/MCKD2). The most frequent cause of this disorder is a mutation in UMOD, the gene coding for uromodulin (Tamm–Horsfall protein) [1–3]. Genetic analysis in this family identified a missense mutation (Cys170Tyr) in the exon 4 of UMOD (Figure 2). This change is predicted to cause misfolding of the protein by removal of a disulfide bridge, leading to abnormal accumulation of mutated uromodulin within tubular cells, and subsequent tubular dysfunction, interstitial fibrosis and slowly progressive renal failure [1–3]. These features were indeed observed in the nephrectomy specimen from the father (Figure 3), which showed areas of tubulointerstitial atrophy with cysts at the cortico-medullary junction. Of note, the proband showed a typical decrease in the urinary excretion of uromodulin (1.1 mg/g creat, for a normal mean value of 9.4 ± 0.33 mg/g creat).

The earliest common manifestation of FJHN is hyperuricaemia caused by increased tubular reabsorption of urate [3]. However, our patient had a serum urate level only in the high-normal range, with a fractional excretion of urate measured twice at 8% and 10%, for a normal value of 12.8 ± 2.9% in females [4]. A recent study in a large number of affected relatives carrying another UMOD mutation revealed that hyperuricaemia was lacking in 8% of them, with affected female patients showing a serum urate level ≤6 mg/dL despite a mild decrease in the fractional excretion of urate [4]. Further studies in young patients with various UMOD mutations should better delineate the range of serum uric acid levels in this disorder.

In summary, the family history provided the crucial clue to the diagnosis of FJHN caused by a mutation in UMOD. In a young patient with a picture of chronic interstitial nephritis, even with a normal serum uric acid level, a family history of chronic interstitial nephritis compatible with an autosomal-dominant transmission should evoke this diagnosis, particularly when hyperuricaemia and/or gout is
Fig. 1. Pedigree of the family. Individuals with renal failure are depicted by black symbols. Circles denote females, squares males.

Fig. 2. Mutation of UMOD. Sequence analysis of the UMOD gene revealed a guanine to adenine transition at nucleotide 510 (c.510G>A) in the exon 4 resulting in the substitution of a highly conserved cysteine by a tyrosine at position 170 (p.Cys170Tyr). This mutation is located in the cysteine-rich domain of the 640 amino-acid uromodulin [1]. Encoded amino acid sequence is indicated above the DNA sequence. Mutated nucleotide is boxed.

Fig. 3. Pathology features and uromodulin accumulation in mutated kidney. (A) Examination of the nephrectomy specimen obtained in the father revealed small cortical and cortico-medullary cysts of which one is large (*) and mainly located in the medulla (Haemalum–eosine). Insert: dilation and duplications of tubular basement membranes of preserved and atrophic cortical tubules, respectively (PAS staining). (B) and (C) Intense immunostaining for uromodulin was detected in a subset of tubule profiles that were enlarged or cystic. At higher magnification (C) the staining for uromodulin is intense and diffusely intracellular. Immunostaining was performed as detailed in [1]. Original magnifications: 10× (A); 160× (B) and 320× (C).
Mild chronic renal failure with a family history of kidney disease is documented in other family members. Establishing the diagnosis of FJHN is relevant for genetic counselling and advising for kidney transplantation [5].

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Conflicts of interest statement. None declared.

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