Autosomal Dominant Tubulointerstitial Kidney Disease Due to *MUC1* Mutation

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Mucin 1 kidney disease, previously referred to as medullary cystic kidney disease type 1, is a rare hereditary kidney disease. It is one of several diseases now termed autosomal dominant tubulointerstitial kidney disease, as proposed by a KDIGO (Kidney Disease: Improving Global Outcomes) consensus report in 2014. Autosomal dominant tubulointerstitial kidney diseases share common clinical findings, such as autosomal dominant inheritance, bland urinary sediment, absent to mild proteinuria, and progressive loss of kidney function. Although the pathophysiology of mucin 1 kidney disease is still under investigation, genetic testing has been developed to detect the most well-known mutation, a single cytosine insertion into a string of 7 cytosines in the variable-number tandem repeat (VNTR) region of the MUC-1 gene. With this diagnostic tool, nephrologists can offer genetic counseling to affected families and monitor closely for progression of disease. We report a Hispanic patient with a strong family history of chronic kidney disease who tested positive for the *MUC1* mutation.

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Teaching Cases focus on interpretation of pathology findings, laboratory tests, or imaging studies to educate readers on the diagnosis or treatment of a clinical problem.

Introduction

Autosomal dominant tubulointerstitial kidney disease (ADTKD) is a group of rare genetic disorders characterized by progressive tubulointerstitial fibrosis and slow decline of kidney function. Four predominant genetic causes have been identified: mutations in *UMOD* (encoding uromodulin), *REN* (encoding renin), *HNF1B* (encoding hepatocyte nuclear factor 1β), and *MUC1* (encoding mucin 1). A fifth gene, *SEC61A1* (encoding the alpha unit of SEC61, a protein that associates with membrane-bound ribosomes), has recently been identified.[1] ADTKD-*MUC1*, or mucin 1 kidney disease (MKD), is a new gene-based terminology proposed by a KDIGO (Kidney Disease: Improving Global Outcomes) consensus conference to replace the previous designation of "medullary cystic kidney disease type 1" (MCKD1) because medullary cysts are uncommonly seen in imaging studies.[2]

The MUC-1 gene, located on chromosome 1q21,[3-5] is a transmembrane protein expressed on the apical surface of many epithelial cells, including in the breast, lung, sebaceous glands, intestine, and distal tubular cells of the kidney. Kirby et al[6] identified a cytosine insertion within one of the variable-number tandem repeat (VNTR) sequences in the *MUC1* coding region as a cause of this inherited condition. This cytosine insertion results in a frameshift mutation leading to the production of a prematurely terminated peptide (MUC-1fs). Yamamoto et al[7] recently discovered another novel frameshift mutation before the VNTR region, resulting a very similar mutant protein. The mechanism by which this *MUC1* mutation produces the phenotype remains poorly understood. Unlike other types of ADTKD, MKD is not associated with hyperuricemia or anemia, making the diagnosis of this rare disease more challenging. To date, approximately 100 affected families have been identified in the United States, but this number may be underestimated due to the difficulties recognizing this disorder.[8] We report a patient of Hispanic origin with a strong family history of chronic kidney disease (CKD) who tested positive for the *MUC1* mutation.

Case Presentation

Clinical History and Initial Laboratory Data

A 41-year-old Hispanic woman from Puerto Rico with a history of gestational diabetes and hypertension was referred to nephrology for newly diagnosed CKD stage 3. The patient had a strong family history of kidney disease. Her mother had end-stage renal disease (ESRD) and was hemodialysis dependent for 13 years before dying at the age of 42 years. One brother presented at age 33 years with uremic encephalopathy and bilateral atrophic kidneys, requiring hemodialysis therapy followed by kidney transplantation. A second brother presented at the age of 32 years for evaluation of CKD stage 3 and was found to have bilateral small renal cysts by ultrasonography and kidney biopsy findings of chronic tubulointerstitial nephropathy (CTIN) with tubular

cysts and tubular basement membrane (TBM) irregularities. A third brother had leukemia diagnosed at the age of 4 years and developed ESRD by the age of 15 years; kidney failure was thought to be related to nephrotoxicity of chemotherapy.

At the time of referral, the patient was asymptomatic, but was found to have elevated blood pressure of 154/96 mm Hg. Physical examination findings were unremarkable. Serum creatinine concentration was 1.4 mg/dL (corresponding to estimated glomerular filtration rate of 44 mL/min/1.73 m^2 by the 4-variable MDRD [Modification of Diet in Renal Disease] Study equation). Urinalysis showed bland urine with a random urine albumin-creatinine ratio of 7.6 mg/g. Other pertinent laboratory results included a mildly elevated intact parathyroid hormone concentration of 75.0 (reference range, 7-53) ng/L, decreased 25-hydroxyvitamin D concentration of 19 (reference range, 20-60) ng/mL, and mildly elevated serum uric acid concentration of 7.3 (reference range, 2.6-7.0) mg/dL. Serologic marker test results, including antinuclear antibody panel and C3 and C4 concentrations, were within the normal range. A

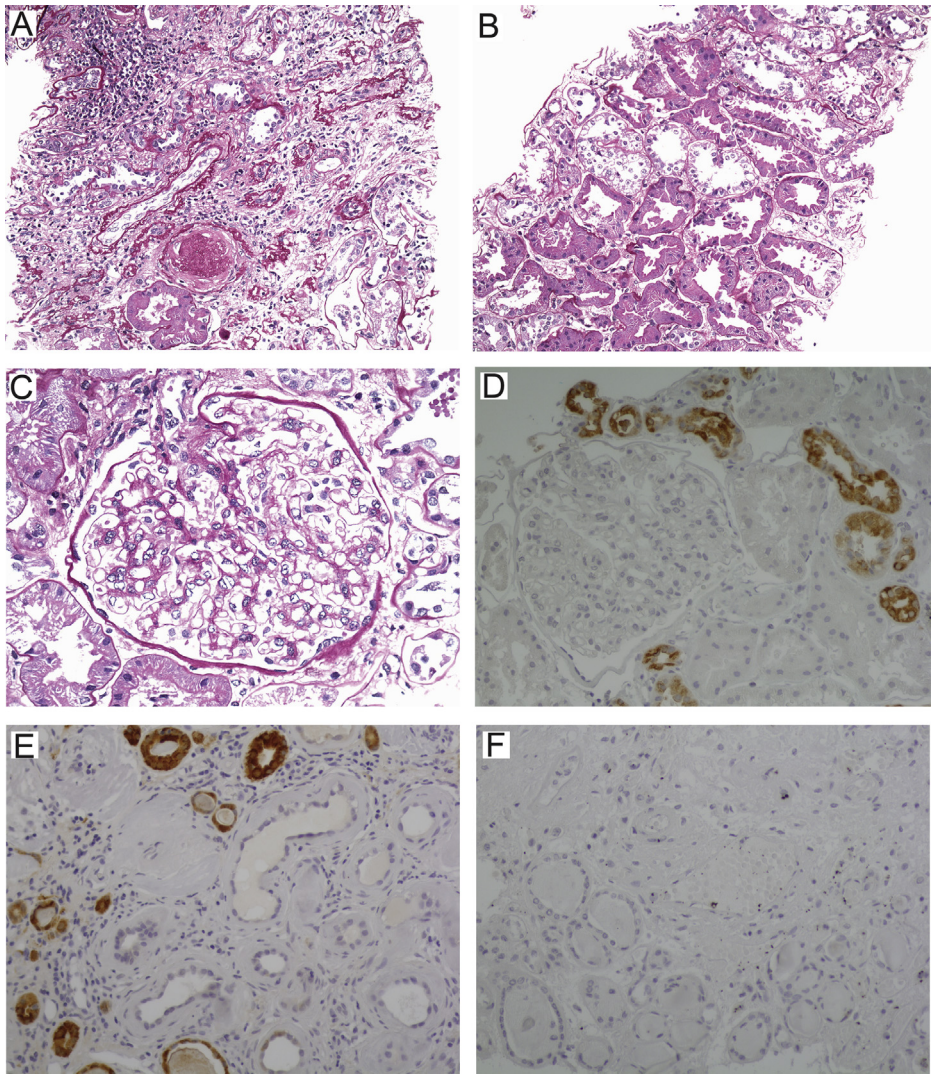

Figure 1. Kidney biopsy findings. Kidney biopsy of the proband patient showed (A) areas of prominent cortical scarring accompanied by scant lymphocytic inflammation intermixed with (B) intact renal cortex exhibiting a normal tubular architecture (A, B: periodic acid–Schiff [PAS]; original magnification, ×200). (C) Glomeruli appear unremarkable (PAS; original magnification, ×400). Formaldehyde-fixed paraffin-embedded kidney samples from the proband, 1 positive control with a known cytosine insertion in the mucin 1 (MUC-1) gene, and 1 negative control (with tubulointerstitial nephropathy but negative for a cytosine insertion in the *MUC1* gene by molecular genetic analysis) were analyzed (see Item S1 for immunodetection methods). Using a custom-prepared rabbit antibody (PA4301), strong intracellular granular staining of MUC-1fs was detected in distal tubules and collecting ducts in kidney tissue from (D) the patient and (E) a positive control (D, E: original magnification, ×200). In samples from the proband and the positive control, there is no staining in the proximal tubules, as would be expected if normal kidney tissue were stained for wild-type MUC-1. (F) Renal tubules were negative for MUC-1fs in kidney samples from the negative control (original magnification, ×200).