CLINICAL VIGNETTE

Autosomal Dominant Tubulointerstitial Kidney Disease due to Uromodulin Mutation

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Case Report

Patient is a 44-year-old male who presents to nephrology for worsened serum creatinine of 2.29 mg/dL. He was initially diagnosed with Chronic Kidney Disease, CKD stage 3a, at age 34 when his laboratory test showed a creatinine of 1.6 mg/dL. He has a family history of chronic kidney disease, with his mother dying from of End Stage Renal Disease, ESRD, and a brother who underwent kidney transplant for ESRD.

Past medical history is also remarkable for gout on allopurinol and obstructive sleep apnea on CPAP. Patient's mother's and brother's etiology of CKD had never been elucidated. His review of system was noncontributory except episodes of acute arthritis in varying joints due to gout flares. His physical examination showed a well-developed, well-nourished, muscular man with normal blood pressure, no signs of fluid retention, no edema. Lungs, heart and abdominal examination were within normal limit and he had no neurological deficits. Laboratory tests showed elevated serum creatinine of 2.29 mg/ld., with normal electrolytes. Urinalysis showed a urine-albumin creatinine ratio of 225 with bland urine sediment. Complete Blood Count, was normal and kidneys and bladder ultrasound was normal.

Given the progressive decline of kidney function, and history of hyperuricemia and gout in the patient, as well as family history of chronic kidney disease of unknown etiology, genetic kidney disease was considered. Autosomal Dominant Tubulo-interstitial Kidney Disease, ADTKD, was most likely and confirmed on genetic testing. The genetic test showed: Autosomal Dominant Tubulointerstitial Kidney Disease with Uromodulin gene mutation, ADTKD-UMOD.

Discussion

Autosomal Dominant Tubulointerstitial Kidney Disease, ADTKD, is a group of genetic disorders with autosomal dominant inheritance that are associated with progressive decline in kidney function.[1] Given the nature of the genetic inheritance, the affected patients have a strong family history of chronic kidney disease in family members. The positive family history, progressive decline of renal function in the setting of bland urine sediment and normal ultrasound of the kidney establish a presumptive diagnosis of ADTKD in this group of patients.[2]

There are several different genetic causes of ADTKD that meet the above diagnostic criteria. The ADTKD-UMOD is one the most common subtypes,[3] and is due to mutation in the UMOD gene encoding Uromodulin, a protein that is produced exclusively in the thick ascending limb of the loop of Henle.[4] Intracellular accumulation of abnormal uromodulin proteins results in tubular cell atrophy and death leading to chronic kidney disease.[4,5] A characteristic feature that distinguishes ADTKD-UMOD from other causes, including ADTKD-REN (REN gene encodes Renin) and ADTKD-MUC1 (MUC1 gene encodes Mucin1), is hyperuricemia and gout at early age. The hyperuricemia is related to decreased uromodulin production, which results in decreased apical expression of the Na-K-2Cl cotransporter in the apical membrane of thick ascending limb of Henle. This results in a mild natriuresis with sodium wasting and volume contraction. The volume contraction initiates compensatory increased sodium and water reabsorption from proximal tubule, which restores volume status to normal. However, this results in a secondary increase in proximal urate reabsorption and hyperuricemia as urate reabsorption follows sodium reabsorption.[6]

Patients with presumptive diagnosis of ADTKD-UMOD, require genetic testing to establish the diagnosis. Given the cost for genetic testing and lack of specific treatment for the disease in some individuals, clinical findings, together with a family history of a reported mutation, suffice for diagnosis. Interstitial fibrosis, tubular atrophy with thickening and lamellation of tubular basement membranes, accumulation of uromodulin protein in the kidney and glomerulosclerosis are the findings seen in kidney biopsy with ADTKD-UMOD. Uromodulin protein can be detected in kidney biopsy by immunostaining using anti-UMOD and may help establish the diagnosis of ADTKD-UMOD.[7] Patient with ADTKD-UOMD should be treated according to established CKD guidelines as there is no specific treatment. Treatment includes management of gout as well as management of progressive CKD.[8]

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