Case Report: Cystinuria and Polycystic Kidney Disease

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abstract

Cystinuria and polycystic kidney disease are 2 genetic disorders that affect the genitourinary tract but rarely together. This case report presents 2 pediatric patients diagnosed with polycystic kidney disease and cystinuria requiring surgical treatment. Both subjects presented acutely with stone disease. Imaging studies and stone analysis established the diagnoses. Although coexistence of these 2 conditions is rare, cystinuria should be considered in the differential diagnosis when evaluating patients with cystic disease who develop renal calculi.

CASE REPORT

Patient A is now a 16-year-old male from Honduras with a 6-year history of nephrolithiasis who originally presented to our institution acutely in September 2012 with a symptomatic 2-mm left ureterovesical junction calculus. His medical history was notable for passing previous calculi at 10 years of age, and his family history was notable for 3 paternal uncles with nephrolithiasis. Computed tomography scans of the abdomen and pelvis without contrast demonstrated bilateral hypoechoic lesions consistent with renal cysts and parenchymal calcifications consistent with nephrocalcinosis. The imaging studies met the criteria for diagnosis of autosomal dominant polycystic kidney disease (ADPKD), although his family history was unavailable. His serum creatinine level was 0.76 mg/dL. The patient was treated conservatively. Unfortunately, he was lost to follow-up until 2013 when he presented with a symptomatic 1-cm left ureteropelvic junction stone with hydronephrosis and a nonobstructing 1.1-cm right stone. He underwent bilateral ureteral stent placement for radiolucent stones. At ureteroscopy 8 weeks later, both stents were completely encrusted with stone debris; he therefore required a percutaneous nephrolithotomy (PCNL) for removal of the encrusted stents. Lost to follow-up again, the patient presented acutely in November 2014 with a large stone burden, including a 2.2 × 1.4 × 1.0 cm left obstructing ureteropelvic junction calculus with hydronephrosis. His serum creatinine level at that time was 0.91 mg/dL. He required 3 separate left PCNL procedures to render his left collecting system stone-free. Stone analysis confirmed 100% cystine stone composition. The patient was referred to pediatric nephrology and was started on tiopronin and potassium citrate therapy, and an angiotensin-converting enzyme inhibitor was eventually added for hypertension. In May 2015, his serum creatinine level was back down to 0.76 mg/dL, and the renal ultrasound at the time demonstrated bilateral parenchymal calcifications without hydronephrosis and multiple cysts. He does not have extrarenal cysts.

Patient B is now a 14-year-old female who originally presented to urology with a large left renal stone in January 2012. She underwent an elective PCNL and subsequent second-look PCNL

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Dr Sidhu drafted the initial manuscript and researched the topic presented; Dr Mittal assisted in drafting the initial manuscript, revised and finalized the manuscript, and was involved in the surgical care of the patients presented; Drs Negroni-Balasquide and Constantinescu reviewed and revised the manuscript and conceptualized the case report, as well as provided the follow-up on the patients reported in the article; Dr Kozakowski conceptualized the case report, took care of the patients surgically, and revised the manuscript; and all authors approved the final manuscript as submitted.

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during the same admission to render her left collecting system stone-free. Stone analysis demonstrated cystine calculi. Her serum creatinine level at the time was 0.76 mg/dL. Pediatric nephrology started her on tiopronin and potassium citrate. A follow-up renal ultrasound in March 2014 demonstrated bilateral renal cysts, meeting the criteria for ADPKD; the patient also had a positive family history. A 24-hour urinalysis demonstrated an appropriate response to medical therapy, based on cystine solubility. A follow-up ultrasound in January 2015 demonstrated bilateral renal cysts, with no evidence of extrarenal cysts or recurrent stones.

DISCUSSION

ADPKD is the most common inherited kidney disease and a common cause of end-stage renal disease in adults. Screening for ADPKD is recommended for individuals with a strong family history and involves imaging. The criteria for diagnosis in patients aged 15 to 39 years include at least 3 unilateral or bilateral cysts. Both of the presented patients fit these criteria according to results of imaging. Patients with ADPKD are known to have an increased risk of nephrolithiasis, likely secondary to both anatomic and metabolic factors.[1] However, cystine stones have rarely been described in these patients. Cystinuria is a rare autosomal recessive metabolic disease causing defective transepithelial amino acid transport in the kidneys. It results in an inability to reabsorb dibasic amino acids (cystine, ornithine, lysine, and arginine) from the glomerular ultrafiltrate, resulting in supersaturation and eventual precipitation of cystine to form calculi.

ADPKD results from mutations in PKD1 on chromosome 16 and PKD2 on chromosome 4. Cystinuria arises from a mutation in SLC3A1 and SLC7A9 on chromosome 2. SLC3A1 has an autosomal recessive inheritance, whereas SLC7A9 exhibits variability in penetrance and clinical presentation.[2] To our knowledge, there is no published evidence of a genetic relationship between cystinuria and cystic renal disease. It is unclear if cystinuria will affect the clinical course of ADPKD or vice versa, as not many individuals have both diagnoses. Further follow-up of these patients could highlight any impact that either disease may have on the other.

Cystine solubility is highly dependent on urinary pH, cysteine concentration, and urinary macromolecules. Cystine crystallizes in physiologic urine, and cystine solubility increases as pH increases. Macromolecules (ie, colloid) also increase cystine solubility. Treatment of cystinuria typically focuses on increasing the urinary cystine solubility through hydration, diet modification, urinary alkalinization, and/or the use of a chelating agent. The typical goal is to lower the urine cystine concentration to <250 to 300 mg/L to decrease stone formation.[3–5] In patients with heterozygote genotypes, the cysteine concentration is significantly higher than in the normal population, but these individuals do not have a higher risk of stone formation, even though the cysteine levels in the urine are high enough to theoretically cause stones. This scenario indicates that the current medical knowledge as it pertains to cystinuria is clearly incomplete. Previous studies have shown that overall compliance with cystinuria treatment and prevention can be poor. Pietrow et al[6] found that only 15% of patients (4 of 26) at a mean follow-up of 38.2 months decreased urine cystine concentration to a sustained level <300 mg/L. Without adequate treatment, patients rapidly develop many stones.

In addition to poor compliance with decreasing the urine cystine concentration, there are additional challenges with treating cystine calculi after they are formed. Cystine stones tend to recur and are frequently bilateral.[7] Percutaneous nephrolithotomy has been performed successfully in children with substantial cystine stone burdens, and it remains a mainstay for treating complex stones. Onal et al[8] achieved stone-free status in 63.1% of renal units (41 of 65 renal units) after PCNL, which increased to nearly 74% after additional endoscopic procedures. However, despite a reasonable stone-free rate after surgical treatment and subsequent continued medical treatment, 31.2% of stone-free patients had a recurrence; 29.4% of patients with residual stone burden on medical therapy experienced regrowth despite medical therapy. These patients should be closely monitored, as untreated cysteine stones may compromise kidney function further and faster in patients with ADPKD.

Love and Yeo[9] previously reported the finding of cystinuria in an adult patient with polycystic kidney disease. This 37-year-old patient also had several renal parenchymal calcifications and was later found on routine follow-up to have hexagonal-shaped crystals on urinalysis and was diagnosed with cystinuria. The investigators postulate that this combination of genetic diseases was likely random.

Koraishy et al[10] described a case of cystic kidney disease forming in a patient who developed systemic toxicity from long-term D-penicillamine use for cystinuria treatment. Their patient presented for acute kidney injury while taking D-penicillamine therapy and was found to have severe bilateral cystic kidney disease. In addition, the patient was found to have other evidence of D-penicillamine toxicity, including skin findings.

D-penicillamine is known to result in improper collagen deposition and function of elastic fibers. The authors postulated that D-penicillamine use produced dysfunction of the extracellular matrix, eventually resulting in cyst formation. Of note, neither of our patients was taking D-penicillamine, or any therapy for cystinuria, when they presented.

ADPKD does not affect the ability to perform purely endoscopic procedures on patients with stone disease. Ureteroscopy, laser lithotripsy, and basket extraction of stones is not different in these patients because the calyces and the ureter are not affected by the ADPKD. Many cystine stones are very large and necessitate percutaneous nephrolithotomy, which requires percutaneous access through the kidney parenchyma. This access can be more difficult in patients with ADPKD and will depend on the relative enlargement of the kidney, the location of cysts, and if the cysts are distorting the calyces. Larger kidneys will require longer access needles, and distorted calyces will make it harder for the radiologist or the urologist to gain access to the collecting system. The course of the access may be changed, based on the location of the cysts, to avoid them if possible; ultimately, the access route will depend on the interventionalist.

This article describes the first cases of coexistent ADPKD and cystinuria reported in children and suggests evaluation for the possibility of cystine stones in patients with ADPKD presenting with nephrolithiasis.

ABBREVIATIONS

ADPKD: autosomal dominant polycystic kidney disease
PCNL: percutaneous nephrolithotomy

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