Recurrent Nephrolithiasis Causing Kidney Failure

Amy A. Yau, Judy Hindi, and Jaime Uribarri

Clinical Presentation

A 56-year-old woman with diabetes mellitus and kidney failure treated by kidney transplantation 3 months prior is referred to your clinic for elevated serum creatinine. She gives a personal history of recurrent urinary tract infections in the setting of obstructive uropathy and recurrent nephrolithiasis. Two years ago, she developed kidney failure. Imaging at the time revealed staghorn calculi with left hydroureter (Fig 1). She underwent bilateral ureteral stent placement with some improvement in glomerular filtration rate (GFR); however, she continued to experience progressive GFR decline and required hemodialysis. At the time of planned dialysis initiation, she also underwent bilateral native nephrectomies owing to persistent pain. Pathology was significant for oxalate nephropathy with nephrolithiasis, diffuse interstitial scarring, and focal global glomerulosclerosis with intratubular birefringent calcium oxalate crystal deposits. She denies a family history of kidney disease or nephrolithiasis.

After a year of treatment with dialysis, she received a living unrelated kidney transplant. One month after transplantation, she had a kidney biopsy performed for elevated serum creatinine. Kidney pathology was significant for inspissation of refractile oxalate crystals in the tubular lumina and in the cytoplasm of renal tubular cells. She was subsequently hospitalized for hyperkalemia (potassium, 5.9 mEq/L) with a serum bicarbonate of 13.6 mg/dL and serum creatinine of 1.52 mg/dL. Serum creatinine remained stable during her hospitalization, and she was discharged on daily oral sodium polystyrene sulfonate with close follow-up.

• What are the causes of oxalate nephropathy?
• What further work-up would you want, knowing the nephrolithiasis led to her kidney failure?
• What is the typical natural history of her disease?
• What are the long-term therapeutic options?

Discussion

What are the causes of oxalate nephropathy?
Crystallization of urinary oxalate and deposition into tissues lead to oxalate nephropathy, and the underlying mechanism is hyperoxaluria owing to increased oxalate intake, increased gastrointestinal absorption, and/or endogenous oxalate overproduction. Excess oxalate damages the proximal tubular epithelium and deposits in kidney parenchyma, leading to inflammation and necrosis. As the GFR falls, plasma oxalate levels increase and cause deposition in other tissues, including the kidney, heart, and bone. This soft tissue deposition can increase risk of mortality owing to cardiac arrhythmias, restrictive cardiomyopathy, nephrocalcinosis, and development of kidney failure.

Figure 1. Noncontrast computed tomography of the abdomen. (A) Right staghorn calculi. (B) Left distal ureteral calculi 1.6 × 1.3 cm with severe hydroureteronephrosis.
Dietary oxalate is found in many sources (Box 1), most notably in spinach, rhubarb, cocoa, and nuts, and the oxalate is excreted renally. The malabsorption of lipids owing to small bowel disorders (such as bowel resection, gastric bypass, and cystic fibrosis) and medications (eg, orlistat) can lead to intestinal hyperabsorption of oxalate. Additionally, antibiotics can reduce *Oxalobacter formigenes* colonies, thereby decreasing colonic breakdown of oxalate and increasing serum oxalate. Genetic conditions such as primary hyperoxaluria (Fig 2) lead to excess oxalate production owing to a defect in glyoxylate metabolism.

Other risk factors include hypocitraturia. Low urine citrate favors the precipitation of oxalate in a high urinary oxalate environment, and medications such as carbonic anhydrase inhibitors can result in metabolic acidosis, which, by increasing proximal tubular citrate reabsorption, will have similar effects. Excess vitamin C intake, more so in men, may increase hyperoxaluria owing to nonenzymatic conversion into oxalate.

**What further work-up would you want, knowing the nephrolithiasis led to her kidney failure?**

A 24-hour urine study for stone risk factor assessment is recommended in patients at high risk for bone mineral disease, patients with chronic kidney disease (CKD), and high-risk stone formers. High-risk stone formers include those with a solitary kidney or with family history of nephrolithiasis, malabsorptive diseases, recurrent urinary tract infections, recurrent stones, gout, or type 1 renal tubular acidosis. Genetic testing is indicated if a 24-hour urine study is indicative of an inherited condition such as primary hyperoxaluria or cystinuria. It can also be considered in children with recurrent stone disease, bilateral nephrolithiasis, and stone disease that leads to kidney failure requiring kidney replacement therapy. Primary hyperoxaluria is suspected when there are recurrences and bilateral kidney stones or urinary oxalate is more than 65 mg/d.

For this patient, a 24-hour urine study was completed and results were significant for hypocitraturia and hyperoxaluria (Table 1). Genetic testing revealed a mutation in *GRHPR*, the gene encoding glyoxylate reductase/hydroxypyruvate reductase, thus narrowing the diagnosis to PH2 (MedGenUID: 120616). The specific mutation is a homozygous guanine-to-adenine substitution at nucleotide 494 of the coding sequence, which is predicted to lead to a glycine-to-aspartate change at amino acid 165 (c.494G>A (p.Gly165Asp)).

**What is the typical natural history of her disease?**

Generally, untreated idiopathic renal calculi have a 50% recurrence rate within 10 years and can lead to CKD and progression of CKD, but progression to kidney failure is rare. The situation is quite different in patients with primary hyperoxaluria. By age 40, about 50% of patients with PH1 and nearly 25% of patients with PH2 reach kidney failure.

**What are the long-term therapeutic options?**

Dietary changes such as increasing fluid intake and decreasing oxalate ingestion may have some effect.
Improving hypocitraturia through drinking citric juices or urine alkalization with oral alkali supplements may help to inhibit calcium oxalate crystallization by binding free urinary calcium and alkalizing urine. Vitamin B6 is a coenzyme for alanine-glyoxylate aminotransferase and may reduce disease progression in 10%-30% of PH1 patients, but it has no role in PH2 owing to the different enzymatic defect. As the affected enzyme is liver-specific, definitive therapy for PH1 is liver transplantation, usually combined with kidney transplantation. Isolated liver transplantation to preempt kidney failure is described in case reports and proposed by some, but isolated kidney transplantation has a high rate of recurrence and allograft failure. The need for liver transplantation in PH2 remains unclear, as there is extrahepatic enzymatic activity, although there is a case report showing benefit in a previously failed kidney allograft.

At the time of last follow-up, the patient is doing well receiving treatment with sodium bicarbonate supplements, with a stable serum creatinine at 1.4 mg/dL.

**Final Diagnosis**
The final diagnosis, established by genetic testing, is autosomal recessive primary hyperoxaluria type 2.

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**References**

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**Table 1. Results of 24-hour urine stone risk study post kidney transplantation**

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**Quiz**

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FELLOWSHIP PROGRAM HIGHLIGHT

Note from editors: To recognize fellowship programs’ educational mission, AJKD is using its popular Quiz feature to highlight Nephrology Fellowship programs when an author is a Nephrology Fellow. To participate, Fellowship Program Directors mentor fellows in submitting prospective Quizes; those that are selected for publication include a brief description of the fellowship program from the Director. At the time of submission of “Recurrent Nephrolithiasis Causing Kidney Failure,” author Amy Yau was a Nephrology Fellow at Mount Sinai.

Program: Icahn School of Medicine at Mount Sinai Nephrology Fellowship Program (https://icahn.mssm.edu/education/residencies-fellowships/list/msh-nephrology-fellowship)

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