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Case Report

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A case of cystinuria with a heterozygous *SLC3A1* mutation presenting with recurrent multiple renal stones in a 14-year-old boy

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Cystinuria, a genetically inherited disorder, is a rare cause of kidney stones. It is characterized by impaired transport of cystine and amino acids in the proximal renal tubule and the small intestine. Most patients develop cystine stones throughout their lifetime. Recurrent renal stones need to be extracted by repeated urologic interventions. Treatment options of cystinuria for preventing stone recurrence are limited and poorly tolerated. In this study, we report a pediatric case of cystinuria with a heterozygous *SLC3A1* mutation diagnosed by stone analysis, measurement of urine cystine excretion, and genetic analysis. There were recurrent renal stones despite repetitive shock wave lithotripsy and retrograde intrarenal surgery. However, the rate of stone formation seemed to be slower after D-penicillamine was added into adequate hydration and urinary alkalinization.

Keywords: Case reports; Cystinuria; SLC3A1 protein, human; Urolithiasis

Introduction

Cystinuria (OMIM 220100) is an inherited disorder characterized by impaired transport of dibasic amino acids including cystine in the brush border membrane of the proximal renal tubule and the small intestine [1]. Because of the low solubility of cystine at normal urinary pH, cystine stones can be caused by high urinary cystine excretion [1-3]. Cystine stones often occur in the second or third decade of life. It can also occur during infancy or childhood occasionally [1]. Its incidence rate in the pediatric age group has increased up to 6%–8% of all stones [4]. However, according to the recent urinary stone composition data from South Korea [5], cystine stones occurred rarely in the Korean population, which accounted for only 0.35% of the total stone composition. Mutations in the *SLC3A1* and *SLC7A9* genes are known to be responsible for cystinuria. Homozygotes or mixed heterozygotes of these two genes are associated with increased urinary cystine excretion and kidney stone formation [6]. Generally, treatment options of cystinuria for preventing stone recurrence are limited and poorly tolerated. Given its prevalence by age, studies about pediatric patients of cystinuria confirmed by genetic analysis are relatively rare. In this study, we report a rare case of a 14-year-old boy with cystinuria caused by a heterozygous mutation in the *SLC3A1* gene with recurrent multiple kidney stones. The rate of stone formation seemed to be slower after D-penicillamine was added into conservative management.

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Case report

A 14-year-old boy was referred to our hospital because of recurrent renal stones with gross hematuria and flank pain. Five years ago, he had sudden onset of sharp pain in his back and lower abdomen with brown-colored urine. After diagnosis of renal stones by urologists, he underwent repeated shock wave lithotripsy every 6 months. However, stones kept occurring alternately on both kidneys with a shortened period of every 3 to 4 months and increases in size and numbers. Retrograde intrarenal surgery of left kidney and that of both kidneys were done to remove large kidney stones at 18-month intervals. There was no family history of urolithiasis or other renal diseases. His body mass index was 20.2 kg/m^2 (32 percentiles) and his blood pressure was 118/61 mmHg (75 percentiles). He did not have any medical history of urinary tract infection. He had taken potassium citrate (10 mEq/dose, 3 times a day) for 6 months. Initial laboratory evaluation was as follows: white blood cell count of 10.6×10^3/μL, hemoglobin level of 14.4 g/dL, platelet count of 273×10^3/μL, blood urea nitrogen of 11.7 mg/dL, creatinine (Cr) of 1.01 mg/dL, sodium of 141 mmol/L, potassium of 4.4 mmol/L, chloride of 105 mmol/L, calcium of 9.8 mg/dL, phosphorus of 3.3 mg/dL, cystatin C of 0.99 mg/L (reference, 0.53–0.95 mg/L), and estimated glomerular filtration rate (eGFR) of 101 mL/min/1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Cr-cystatin equation. Urinalysis showed pH 6.0, +/– protein, and >60 red blood cells/high-power field. Urinary levels of calcium, uric acid, citric acid, and oxalate were 32 mg/day (reference, 100–300 mg/day), 355 mg/day (reference, 250–750 mg/day), 573 mg/day (reference, 320–1,240 mg/day), and 27 mg/day (reference, <50 mg/day), respectively. A renal sonogram and abdomen computed tomography showed multiple, hyperechoic stones on both kidneys without hydronephrosis (Fig. 1). The diagnosis of cystinuria was confirmed by highly elevated urinary levels of cystine and dibasic amino acids. Urinary concentrations of cystine, ornithine, lysine, and arginine were 943 μmol/g Cr (reference, 25–125 μmol/g Cr), 1,387 μmol/g Cr (reference, 31–91 μmol/g Cr), 5,907 μmol/g Cr (reference, 153–634 μmol/g Cr), and 3,212 μmol/g Cr (reference, 31–109 μmol/g Cr), respectively. Chemical stone analysis using colorimetric method was positive for cystine composition. Urine alkalinization with potassium citrate (30 mEq/day), oral hydration (>3 L/day),

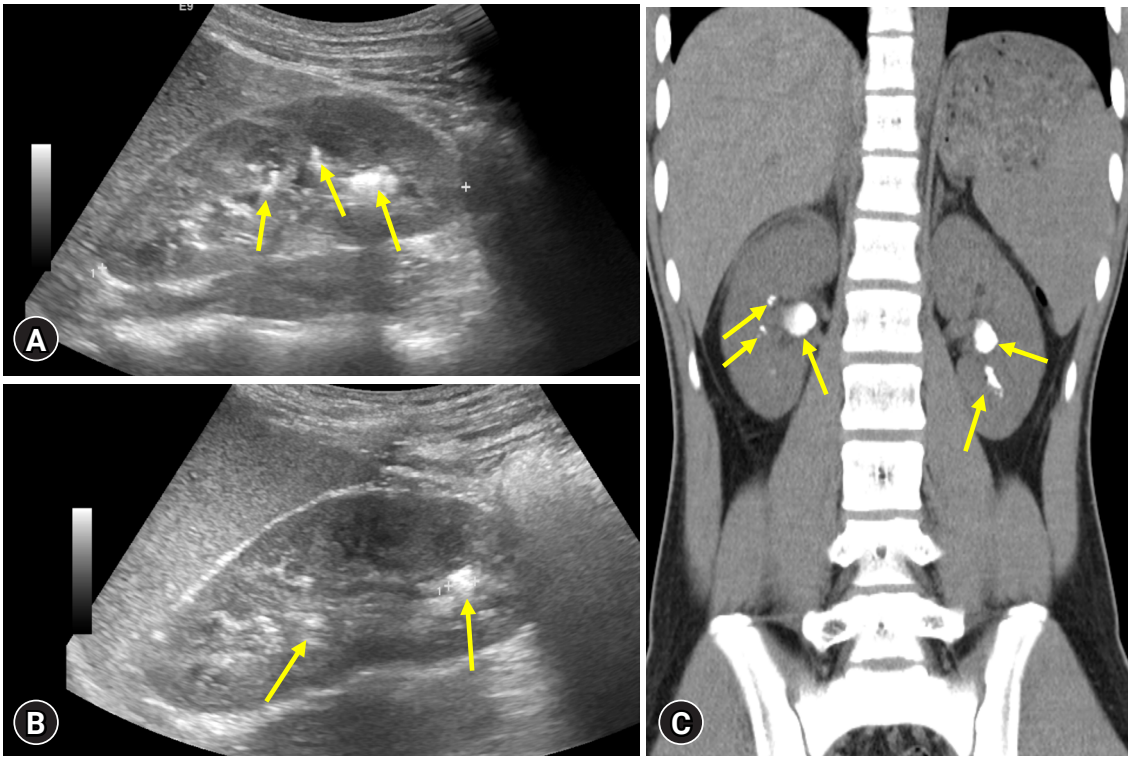

Fig. 1. Renal ultrasonography and abdominal computed tomography showing multiple kidney stones. (A) Right kidney. (B) Left kidney. (C) Multiple hyperechoic stones in bilateral pelvicalyceal system (arrows). The largest sizes of renal stones on right kidney and left kidney were 1.53 cm and 0.62 cm, respectively.

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and a low-protein (<20 g/day) and low-salt (<2 g/day) diet were initiated for the management of cystinuria simultaneously. Despite repeated interventions and supportive care, stones recurred continuously. In addition, metabolic alkalosis occurred intermittently due to prolonged high-dose citrate therapy. After regular follow-ups for a year, he and his parents underwent genetic analysis using whole exome sequencing and heterozygous *SLC3A1* gene mutations [NM_000341.4:c.1820del (p.Leu607HisfsTer4)] were found in the patient and his mother (Fig. 2). Due to recurrence of kidney stones, captopril (12.5 mg/day), the first angiotensin-converting enzyme inhibitor that has a sulfhydryl ligand that forms bond with cysteine, was added in addition to standard fluid and alkalization therapy. However, after a month, multiple kidney stones started to recur again. Captopril was stopped since it seemed not to be effective. Instead, D-penicillamine (250 mg/day) was started and he got percutaneous nephrolithotripsy to remove stones at the same time. After that, renal stones were reduced without newly visible stones. There was no gross or microscopic hematuria for 6 months. Serum cystatin C level gradually increased in the last 2 years (0.99, 1.03, 1.00, 1.22 mg/L) and the latest eGFR using the CKD-EPI Cr-cystatin equation was 87.0 mL/min/1.73 m^2. The patient's clinical course over the 2 years of treatment is shown in Fig. 3.

Discussion

Here we report a case of cystinuria with a heterozygous *SLC3A1* gene mutation in an adolescent boy with recurrent multiple renal stones. Cystinuria was diagnosed by stone analysis, measurement of urine cystine excretion, and genetic analysis. While repeated urologic interventions were needed, D-penicillamine was found to be effective in decreasing the rate of stone formation without any side effects in our case.

Cystinuria is an inborn congenital disorder characterized by impaired transport of dibasic amino acids including cystine which is relatively insoluble at the physiological pH of urine [1]. As a result, it can produce cystine stones, causing pain, hematuria, infection, and renal failure in rare cases. The diagnosis of cystinuria is based on confirmation of a hexagonal cystine crystal with a microscopic examination of urine. However, this can only be observed in about 25% of patients. The most obvious diagnostic method is to confirm an increase in cystine excretion in 24-hour urine tests. However, since it is difficult to collect 24-hour urine in infants, one-time urinary cystine to Cr ratio can help diagnose it [7]. Cystine stones are very large in size, and they recur frequently. Thus, they are difficult to treat with interventions. Therefore, early diagnosis and preventive treatment are important. Current medical management to reduce stone formation for cystinuria includes adequate hydration (>3 L/day), low sodium (<2 g/day) and protein (<20 g/day) diet, and urine alkalinization (up to pH 7.5) [8]. If these measures fail, cystine-binding thiols such as tiopronin and D-penicillamine, captopril, and crystal growth inhibitors can be considered [8]. Due to recurrent episodes of renal stones, patients with cystinuria are at high risk of developing chronic kidney disease [9].

Although genetic testing is not always required for the diagnosis of cystinuria, it might be helpful in diagnosing patients with atypical clinical presentation and genetic counseling. Previous studies have shown that cystinuria is caused by mutations in the *SLC3A1* gene (located on chromosome 2p21) encoding neutral and basic amino acid transport protein rBAT

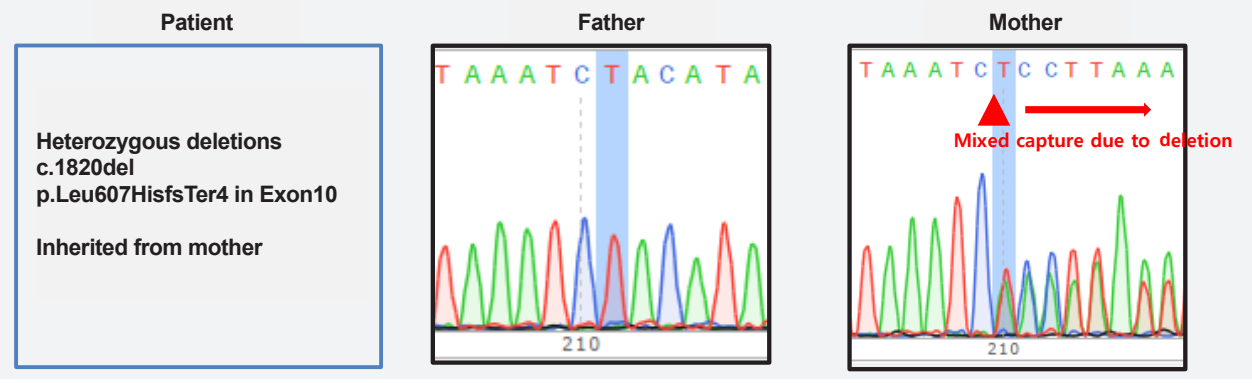

Fig. 2. Electropherogram showing the heterozygous *SLC3A1* gene mutation.

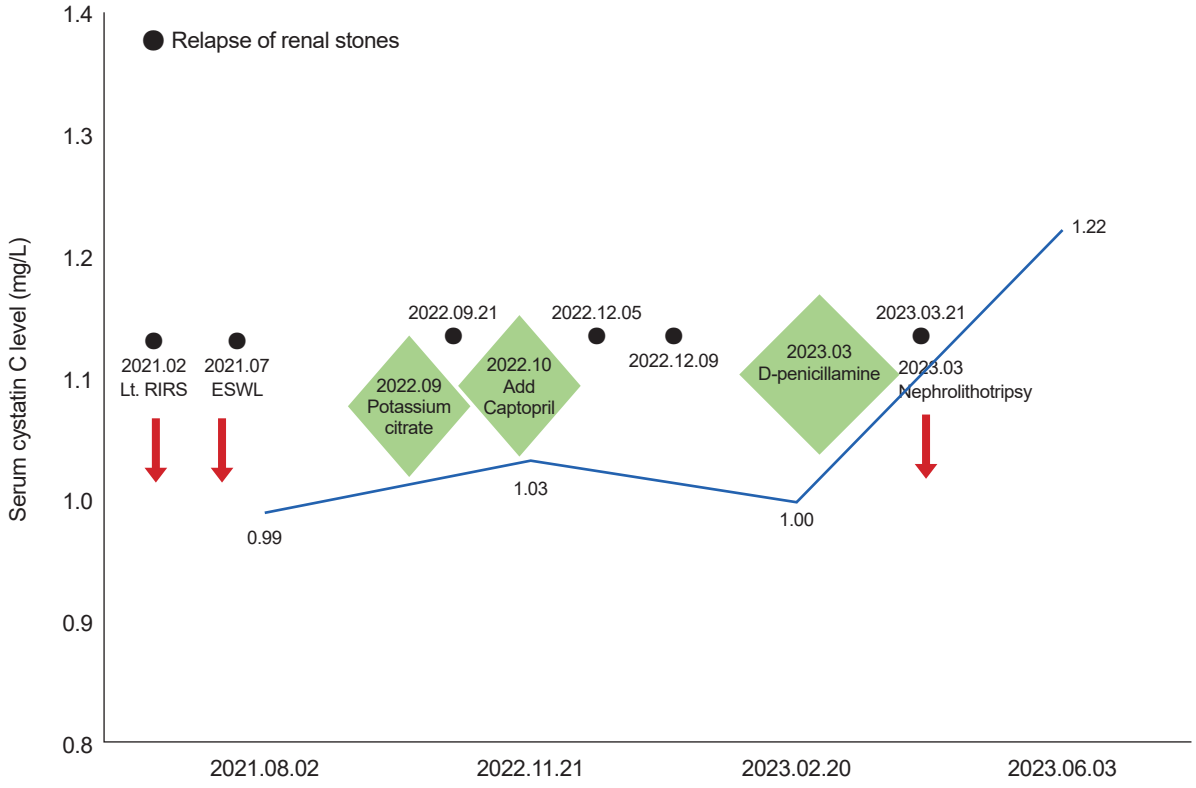

Fig. 3. Clinical course of the patient over 2 years of treatment. RIRS, retrograde intrarenal surgery; ESWL, extracorporeal shock wave lithotripsy.

and the *SLC7A9* gene (located on chromosome 19q13) encoding b(0,+)-type amino acid transporter 1 [6]. According to mutation types of these two genes, cystinuria can be classified into type A (two mutations on *SLC3A1*), type B (two mutations on *SLC7A9*), and type AB (one mutation on each of *SLC3A1* and *SLC7A9*) [1,6]. Jeong et al. [10] identified six new mutations in mutational analysis of Korean cystinuria patients, and the mutations in the *SLC3A1* gene were more frequently observed in the Korean population. Our case belongs to type A cystinuria since the patient's genetic analysis showed a heterozygous *SLC3A1* gene mutation. While type AB patients are known to have a mild phenotype, the disease severity in relation to the type of cystinuria cannot be correlated in pediatric patients [1,7]. A recent study of genotypic and phenotypic analyses of Korean pediatric patients with cystinuria did not find a significant association between clinical course and genotype [7]. In that report [7], the prevalence of cystinuria was higher in females with a median onset age of 1.5 years. Only one patient with a heterozygous *SLC7A9* mutation had a family history of renal stones. Among eight patients, except for one patient with a single heterozygous *SLC3A1* mutation who was treated with oral sodium bicarbonate only, seven patients were treated with tiopronin combined with potassium citrate or captopril. Most patients had to undergo repeated urologic interventions similar to our case. However, symptoms of cystinuria of our patient developed at a relatively older age. In particular, the onset age of a patient with a heterozygous *SLC3A1* gene mutation in the study of Kim et al. [7] was 1.3 years. While the patient showed therapeutic effect with conservative management only, our patient had to constantly change treatment strategies because of recurrent renal stones.

It has been widely recognized that the most effective therapy in patients with cystinuria is to prescribe thiol-containing compounds including α-mercaptopropionyl glycine (α-MPG) and D-penicillamine [8]. Thiol compounds contain sulfhydryl groups, which undergo a disulfide exchange reaction with cysteine, generating two molecules of cysteine bound to thiols. The solubility of the complex is 50 times higher than cystine [8]. Tanzer et al. [11] have reported a case of cystinuria in a 1-year-old girl with a heterozygote for *M467T* mutation within the *SLC3A1* gene. She underwent repeated nephrolithotomy and

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received α-MPG. Tangnararatchakit et al. [12] have also shown successful management with D-penicillamine in 4-year-and 6-month-old girls with cystinuria after recurrent stone removals. Most pediatric cases did not have a history of familial kidney diseases. They initially presented with symptoms of fever, abdominal pain, and vomiting [7,11,12]. Although repeated urologic interventions were done with conservative treatment, renal stones frequently recurred. Therefore, cystine-binding thiol drugs or captopril in addition to urine alkalinization were added. These concurrent treatments led to success with disappearance of renal stones in follow-up examinations. Similar to these cases, treatment for cystinuria was also difficult in our case. Drugs sometimes had to be discontinued or replaced by other drugs in consideration of the patient's treatment compliance, drug side effects, and treatment effects. Conservative management with potassium citrate was not effective. Therefore, we added captopril to induce formation of captopril–cysteine disulfide known to be 200 times more soluble than cystine [8]. However, the dose of captopril could not be sufficiently given due to the risk of hyperkalemia. There was a concern for the development of hyperkalemia since we were also using potassium citrate in our patient. As a result, multiple renal stones recurred and urological procedures had to be repeated. Then D-penicillamine was administered by gradually increasing its dose. There has been no recurrence of newly formed renal stones for 6 months. D-penicillamine forms penicillamine-cysteine disulfide through thiol-disulfide exchange reaction so that cystine could not be crystallized in the urine. Halperin et al. [13] have revealed the efficacy of D-penicillamine which enables significantly less urinary tract surgery for stone removal and reduces episodes of renal colic. However, it can cause changes in appetite, skin mucosal lesions, proteinuria, systemic lupus erythematosus, and blood abnormalities such as leukocytosis and thrombocytopenia [1,14]. Due to these side effects, patients' drug compliance is often low. In order to increase patient's compliance with treatment, it is important to determine the appropriate dose of the drug that can minimize the concentration of cysteine in urine while reducing side effects of the drug. In addition, regular blood tests and urine tests are needed to monitor drug's side effects as well as progress of the disease. In spite of dietary and conservative treatments mentioned earlier, if the treatment response is refractory, α-MPG (tiopronin) can be applied to reduce free cystine concentration. It has a similar mechanism of action to D-penicillamine with fewer side effects, including nausea, vomiting, diarrhea, skin rash, etc. Jung et al. [9] have shown that α-MPG can reduce individual stone formation rate in cystinuric patients showing toxicity of D-penicillamine. As tiopronin is currently unavailable in South Korea [9], we used D-penicillamine instead of tiopronin.

Previous studies [1,14] have shown that patients with cystinuria are at risk of acute kidney damage and rapidly progressing chronic renal failure. Prot-Bertoye et al. [15] have suggested that recurrent renal stones with cystinuria extracted by repeated interventions might deteriorate kidney function with an eGFR of <60 mL/min/1.73 m^2. Furthermore, a few patients can progress to end-stage kidney disease. The key mechanism of impaired renal function in cystinuria is insolubility of cystine in the tubular fluid and urine. At the histological level, cystine crystals can cause obstruction in ducts of Bellini and lead to interstitial inflammation/fibrosis [11]. In our patient, the level of cystatin C, a useful biomarker for eGFR over serum Cr, gradually increased in the last 2 years. Continuous close monitoring for kidney function and therapy to prevent cystine stone events are of utmost importance.

In summary, cystinuria is a relatively rare disease in children. It is difficult to diagnose early due to its non-specific symptoms. In addition, although medical treatment is inevitable because of a low therapeutic effect only with dietary and conservative treatment, there are many difficulties considering drug's side effects and patients' compliance to treatment. Here, we report a rare case of a 14-year-old boy with cystinuria caused by a heterozygous *SLC3A1* mutation showing recurrent multiple renal stones. The rate of stone formation seemed to be slower after D-penicillamine was added. Since there were frequent urological procedures and relapses of urinary stones in our patient, continuous monitoring for kidney function is needed. In the future, studies including multicenter and large-sized participants are needed for successful preservation of renal function and comprehensive management approach in patients with cystinuria.

Ethical statements

This study was approved by the Institutional Review Board of Korea University Ansan Hospital (IRB No. 2023AS0226). Informed consent was waived due to its retrospective study design.

Conflicts of interest

Hyung Eun Yim, an Editor-in-Chief of the journal, was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflict of interest relevant to this article was reported.

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Author contributions

Conceptualization: HEY
Data curation: MHS, HEY
Formal analysis: HWC, HEY
Methodology: HWC, MHS, HEY
Project administration: HEY
Visualization: HWC, HEY
Writing - original draft: HWC, HEY
Writing - review & editing: HWC, MHS, HEY
Approval of final manuscript: all authors.

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