




## Unusual Cause of Nephrolithiasis: Cystinuria

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**ABSTRACT** Cystinuria is a rare hereditary disease in which excretion of detectable amount of cysteine, lysine, ornithine and arginine amino acids in the urine is present leading to cysteine nephrolithiasis. Over 100 mutations for SLC3A1 and SLC7A9 genes were identified for this disease. 47 years old male patient suffering from recurrent nephrolithiasis analysis of which revealed L-cysteine type stone for the last 12 years applied to our hospital with the complaint of flank pain. Obesity, hyperglycemia, hypertriglyceridemia, microscopic hematuria, macroalbuminuria, multiple stones in the urinary tract with the diameter of 1 cm and hypercystinuria were detected. Urology consultation for stone removal, alkalization and increasing the volume of urine, life style modifications in order to lose body fat, potassium citrate and tiopronine were advised to the patient. If stones passed through urinary tract are not analysed, diagnosis of cystinuria will be missed out. With this case, an unlucky but common state for patients with cystinuria is discussed.

**Keywords:** Cystinuria; nephrolithiasis; tiopronine

Cystinuria with the overall prevalence of 1 person per 7.000 population is an autosomal-recessive defect in reabsorptive transport of cysteine and dibasic amino acids ornithine, arginine, and lysine from the luminal fluid of the renal proximal tubule. Two genes SLC3A1 (located on chromosome 2p16.3-p21) and SLC7A9 (located on chromosome 19q12-13.1) are responsible for cysteine reabsorption. Mutations of these genes lead to inability of renal tubules to reabsorb cysteine and phenotypic manifestation of cystinuria. The relative insolubility of cysteine at physiological urine pH lead to stone formation, infection, obstruction and ultimately chronic kidney disease.<sup>1,2</sup> The other dibasic amino acids including ornithine, arginine and lysine are soluble, so increase in their urinary excretion does not lead to stones. Cystine stones which occur most commonly within the first two decades of life are found in 6-8% of pediatric renal lithiasis cases while 1-2% of adult stone formers.<sup>2</sup> The median age of onset of stones was reported as 12 years.<sup>3</sup> The appropriate management of cystinuria is often challenging and requires close follow-up of the patient.

Here, recurrent cystine stone former 47 years old man with no sign of urolithiasis until 35 years of his life was presented.

## CASE REPORT

A 47 years old male patient who gave informed consent for publishing his medical information was presented to nephrology clinic with the complaint of flank pain and dysuria with recurrent spontaneous urinary stone passage frequency of which was increased in the last two years. He had five previous urological interventions in the past history. It was learned from his anamnesis that he had first nephrolithiasis attack at the age of 35 years old and just two years ago analysis of calculus composition (with radiograph diffraction method) performed by Laboratories of General Directorate of Mineral Research and Exploration confirmed as cysteine stone. There was no consanguinity between his parents. Hydration, nonsteroidal anti-inflammatory drugs and multiple urological procedures like stents have been attempted but pain of the patient was not relieved. On the contrary during last two years, intensity and frequency of the pain was worse and even negatively influenced patient's sleeping quality. The patient had body mass index of 31.6 kg/m<sup>2</sup> and smoking (1 packet/day) history for 17 years. His blood pressure was 110/70 mmHg in both arms, there was no costovertebral angle tenderness in physical examination. In his laboratory evaluation, acidic urine pH (5.5), microscopic hematuria, hyperfiltration (creatinine clearance of 149 mL/min), macroalbuminuria (urine albumin (mg)/creatinine (mg) ratio:0.45; protein (mg)/creatinine (mg) ratio: 0.65), fasting hyperglycemia (120 mg/dL), hypertriglyceridemia (569 mg/dL), low HDL-cholesterol levels (39 mg/dL) were found. Noncontrast computerized tomography showed multiple stones (the biggest one with diameter of 1 cm) in right kidney (Figure 1) while stones were invisible (non radiopaque) in the plain X-ray of kidneys, ureters and bladder (KUB) (Figure 2). Analysis of the stone which passed spontaneously a month ago was again positive for cysteine (Figure 3). The amount of urinary cysteine excretion measured in two different laboratories from the same urine sample was found to be 299 mg/L (899 mg/day) and 1080 mg/L (3348 mg/day) respectively (normal level is less than 30 mg/day,

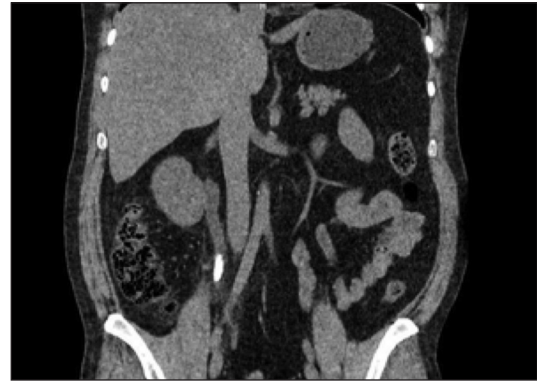


FIGURE 1: Noncontrast computerized tomography image showing the biggest stone.



FIGURE 2: Normal plain X-ray of kidneys, ureters and bladder.



FIGURE 3: Macroscopic view of cysteine stone.

limit of solubility is 243 mg/L).<sup>4-6</sup> With these findings, patient was diagnosed as metabolic syndrome and cystinuria. Urology and endocrinology consultants were advised to the patient. Life style changes (cessation of smoking, diet for diabetes and obesity, regular exercise, hydration), potassium (not sodium) citrate in order to get alkaline urine pH (7-7.5) and tiopronine (Thiola) 3\*200 mg were prescribed.

## DISCUSSION

Different types of crystals make up renal stones. So it is very important to analyze the composition of the stone in order to target the treatment against the specific cause. Removal of an existing stone does not prevent further stones from forming as in our case. The only prevention strategy depends on the lifestyle changes and specific medications which differ according to stone composition. Repeated stone formation necessitates urologic interventions, which mainly include minimally invasive procedures.

Cysteine stones form in people with a hereditary disorder that causes the kidneys to excrete too much of certain amino acids (cystinuria). Cystinuria is more severe in males than in females. In 2006 Dello Strologo and Rizzoni proposed a definition of cystinuria: patients with cystine stones if an increased urinary excretion of dibasic amino acids is noted, or both alleles of 1 of the 2 genes involved are identified, or patients without urinary stone if urine cystine excretion exceeds 1300 mmol/g creatinine (150 mmol/mmol creatinine) or the sum of COLA (cystine, ornithine, lysine and arginine) excretion through the urine exceeds 5900 mmol/g creatinine (8670 mmol/mmol creatinine) in a 24 hour urine sample can be diagnosed as cystinuria.<sup>7</sup> With presence of both cystine stone and increased urinary cystine excretion, our patient was diagnosed as cystinuria. Genetic mutation of our patient was not identified. Genetic analysis is not always necessary for diagnosis of cystinuria.<sup>7</sup> It is needed for classification of cystinuria.<sup>2</sup>

Patients with cystinuria have recurrent renal stones causing significant morbidity, including

pain, recurrent infections, decreased renal function due to recurrent obstruction.<sup>8</sup> Cystinuria is a chronic condition with no cure. So lifelong treatment focuses on mainly prevention which includes reducing the absolute amount and increasing the solubility of the poorly soluble cystine molecule in the urine. For reducing absolute amount of cystine in the urine, limiting dietary sodium and animal protein intake is suggested; for increasing solubility of cystine in the urine, increasing fluid intake, urinary pH and reducing cystine to more soluble cysteine is recommended.<sup>2</sup> For this purpose, D-penicillamine and tiopronin (α-mercaptopropionylglycine, α-MPG) are the most commonly used agents.<sup>9</sup> As cystine is the homodimer formed from the linkage of two cysteine molecules by a disulfide bond, thiol-containing drugs (eg, tiopronin given at doses of 400 to 1200 mg/day, administered in three divided doses) have sulphhydryl groups that can reduce this disulfide bond, producing mixed drug-cysteine disulfides that are more soluble than the homodimer cystine. The aim of all these medical therapy is to maintain the cystine concentration in the urine below its solubility level. The limit of solubility can be conservatively estimated as approximately 243 mg/L (1 mmol/L), provided the urine pH is 7 or higher. A urine cystine concentration below this level will usually prevent cystine crystallization and may lead to dissolution of existing crystals.

In the literature, similar cases were reported however first symptoms were noticed at younger ages in these cases (13 years old) than our patient (35 years old).<sup>10</sup> The patients were prescribed sodium bicarbonate and potassium citrate, high fluid intake and multiple urological interventions for removal of stones were performed. Like our patient, stone passage continued in these cases for many years till stone and urine analysis were made.

In conclusion, all patients presenting with new onset of nephrolithiasis should have stone composition determined when possible. Cornerstone of the cystinuria treatment remains stone prevention with hyperhydration, urinary alkalization, and specific pharmacologic therapy.

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### Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

### Authorship Contributions

**Idea/Concept:** Kübra Kaynar; **Design:** Kübra Kaynar, Onur Küçük, Canan Şehit; **Supervision/Consultancy:** Kübra Kaynar; **Data Collection and/or Processing:** Kübra Kaynar, Onur Küçük, Canan Şehit; **Analysis and/or Interpretation:** Kübra Kaynar, Onur Küçük, Canan Şehit; **Source Search:** Kübra Kaynar, Onur Küçük, Canan Şehit; **Article Writing:** Kübra Kaynar, Onur Küçük, Canan Şehit; **Critical Review:** Kübra Kaynar, Onur Küçük, Canan Şehit; **Sources and Funding:** Kübra Kaynar, Onur Küçük, Canan Şehit; **Ingredients:** Kübra Kaynar, Onur Küçük, Canan Şehit.

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