Extremely rapid stone formation in cystinuria: look after dietary supplements!

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ABSTRACT

Cystinuria is an autosomal recessive disease characterized by recurrent nephrolithiasis. The prevention of new stones is based on diluting and alkalinizing urine as well as a low salt and moderate protein intake. The avoidance of food rich in methionine (the precursor of cystine) is also advocated. We report the case of a young adult adherent to the preventative strategy who was stone-free and within months formed a large stone. This coincided with the recent intake of a dietary supplement containing both cystine and methionine. Patients and physicians should be aware of the potential harm of such supplements in patients with cystinuria.

Keywords: amino-acid, cystine, cystinuria, kidney stone, methionin, nephrolithiasis

BACKGROUND

Cystinuria (OMIM 220100) is a rare genetic disease characterized by recurrent stones in the urinary tract. Cystine is filtered by the glomerulus and normally reabsorbed in the proximal tubule through a transporter made from 2 subunits rBAT and $b^{0,+}$AT encoded by the *SLC3A1* and *SLC7A9* genes, respectively. Mutations in these genes underly cystinuria (1). Because cystine is poorly soluble at a urine pH under 7, the excess of urinary cystine results in recurrent cystine stones. Alkaline hyperdiuresis is therefore the cornerstone of the management of these patients (1). Generous fluid intake should induce a urine output large enough to maintain a cystine concentration below 250 mg/L. Dietary adaptations are also needed such as low salt and moderate protein diet (1 g/kg/day). Patients are also advised to avoid foods with a high content in methionine, in order to lower cystine production. Such foods include emmental cheese, horse meat, dried cod or oily fish. (1)

CASE REPORT

A 22-year old patient with genetically proven cystinuria (homozygous *SCL3A1* mutation c.1400 T >C) had a history of kidney stones since the age of 16, with acute renal colic episodes in May 2015, February 2018 and April 2019. After extracorporeal shockwave lithotripsy (ESWL) in August 2019, the patient was stone free in September 2019 (Figure 1 A). The last 24-hour urine sample in July 2019 was as follows : urinary output of 1.2 liter with an estimated intake of 11 g of NaCl/day and protein intake of 0.9 g/kg/day. Urinary pH was 8 with oral supplements of sodium bicarbonate 3 grams/day. Previous urinary pH measurements were 7 and 8.5. The cystine urinary concentration was 490 mg/L. She presented at the Emergency room in January 2020 for recurrent lumbar pain. The ultrasound revealed a 15 millimeter stone in the left renal pelvis, causing hydronephrosis. A double J stent was inserted. The low dose CT confirmed the left pelvicalyceal stone (Figure 1. B). A retrograde utereroscopy was performed with vaporisation. The stone has a typical macroscopic aspect of cystine stone.

Further inquiry, prompted by this rapid stone formation in a recently stable, stone-free patient, revealed the recent start of a food supplement (Novophane®) prescribed by her dermatologist for hair loss. This complex contains 100 mg of cystine and 100 mg of methionine per pill. She took this twice a day from October to November

DISCUSSION

Cystinuria is the most frequent monogenic cause of kidney stone and accounts for 1% and 5% of nephrolithiasis in adults and children respectively (1). In a French cohort (2), the median age at onset of symptoms was 16.7 years, consistent with our case. Our patient had

two more renal colics 35 and 49 months later, respectively. In patients with nephrolithiasis, the number of new stones in a patient denotes the clinical activity of the stone disease. Metabolic activity on the other hand refers to an active crystallization-driving process leading to the formation of new stones or to the growth of existing ones. There is no reliable marker of this metabolic activity. For example, a recurrent calcium stone former, who has passed many new stones in a relatively short period of time, should be considered as metabolically active (3). Our patient was not considered as a clinically or metabolically active stone former. Even though her metabolic parameters were not well controlled in the last lab tests (a low urinary daily output (< 3 liters/day); a high salt intake (> 6 grams/day) leading to a urinary cystine concentration twice above the target (> 250 mg/L)). Her urinary pH and protein intake were in the advised ranges. Her previous urinary cystine concentrations were 720 mg/l in July 2015; 340 mg/l in December 2015 and 70 mg/L in July 2018 showing despite her urinary cystine concentration often above the target concentration, she only occasionally had renal colic. This suggested a new factor was involved in the very fast (4months) formation of a large stone. The use of a food supplement with a high content of methionine and cystine very likely explains this rapid stone formation Admittedly we did not measure urinary cystine during the intake of this supplement Finally, this case highlights the importance of considering an external source of cystine in patients with rapid stone formation. Patients and physicians should be aware of the potential harm of this type of dietary supplements, whose intake has become very popular in the western world (4) in patients with cystinuria.

PATIENT CONSENT

Authors confirm that written consent for publication of the case report was obtained from the patient.

ACKNOWLEDGEMENTS

Committee (Comité d'Ethique Hospitalo-Facultaire Saint-Luc) approved this study (approval number 2020/03JUL/357)

CONFLICT OF INTEREST STATEMENT

None declared.

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Legends to figures and Figures

FIGURE 1 A. Stone free low-dose unenhanced CT - september 2019 (120KVp, 40mAS, DLP 141.7 mGy*cm), MRP coronal reconstruction.

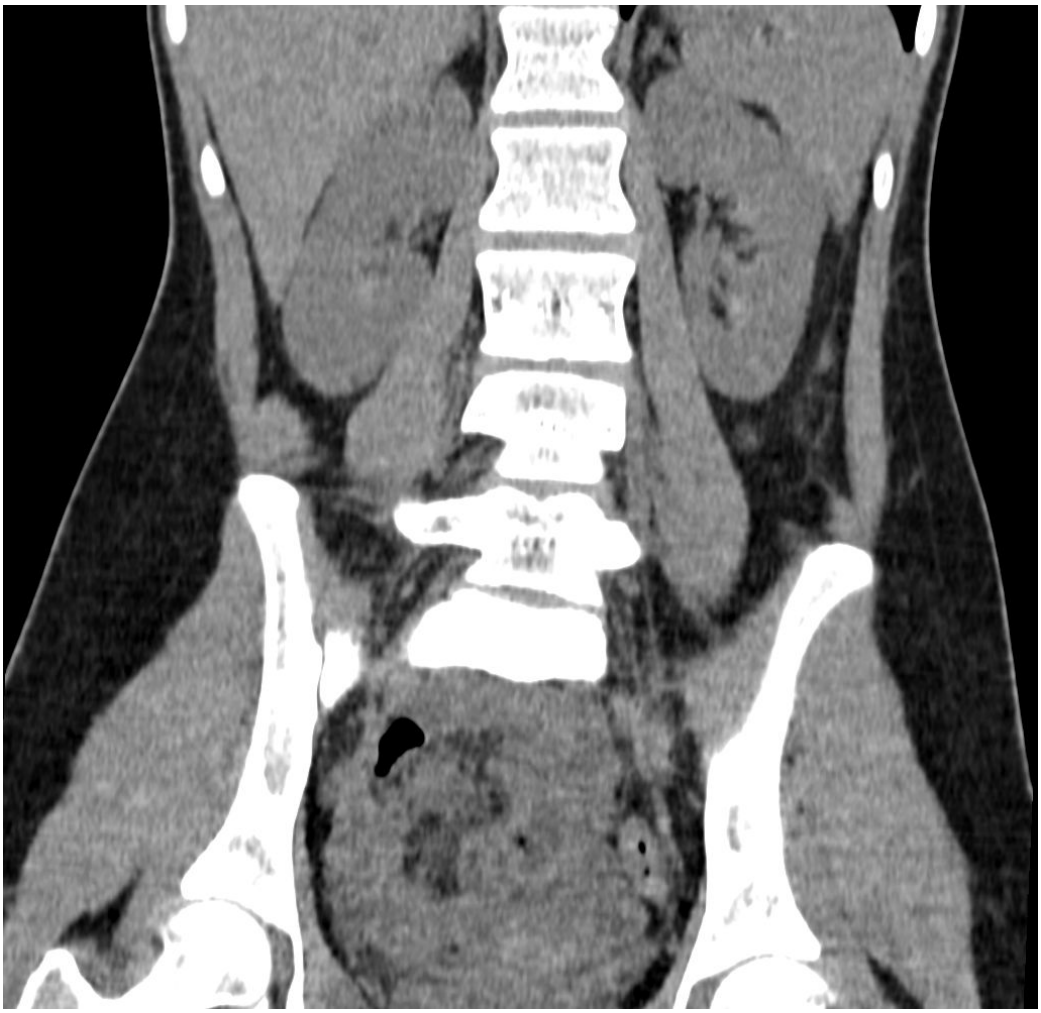

Figure 1 B. Follow up low-dose unenhanced CT – February 2020 (120KVp, 40 mAs, DLP 146.3 mGy*cm) shows a 15 mm left kidney stone (arrow) next to the double J stent (arrowhead)