Cystine Urinary Lithiasis in Thailand : A Report of Five Cases

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Abstract

Cystine urinary stone is an autosomal recessive hereditary disease, frequently recurring and resisting fragmentation by Shockwave lithotripsy. As cases have never been reported before in Thailand, five cases of renal cystine stones at Ramathibodi Hospital were reported. Two were in the same family. In all cases the stones were removed by open surgery or percutaneous nephrolithotomy. Postoperatively, all the stones were analyzed by infrared spectroscopy for cystine. In two cases, cystine stones were also identified by scanning electron microscopy. Urine was analyzed for cystine by sodium cyanide-nitroprusside test, its concentration by spectrophotometry and cystine crystals were identified by the new crystal induction technique under light microscopy. By high-performance liquid chromatography (HPLC) test, urinary dibasic amino acids (ornithine, lysine, arginine) in these cases were also found to be significantly elevated. Clinical findings, diagnosis, treatment and prevention of cystine stones are reviewed.

Key word : Cystine Stone, Crystal, Cystinuria, Infrared Spectroscopy, Sodium Cyanide Niroprusside, Spectrophotometry, Scanning Electronmicroscopy, Urinary Dibasic Amino Acids, Lithotriptor

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The cause of cystine urinary lithiasis is cystinuria, one of the most common inherited metabolic diseases, in which there is an increase in urinary excretion of the dibasic aminoacids:- cystine, ornithine, lysine and arginine (COLA)[1,2]. The disease is a complex autosomal recessive hereditary defect with the mutant genes in the short arm of chromosome two[3], consequently causing a transport defect in the proximal convoluted tubules of the kidney and impaired intestinal absorption of these amino acids [4]. Cystine crystal shows poor aqueous solubility at normal urinary pH. In cystinuric lithiasis, urinary cystine level is higher than 300 mg/L, cystine stones are common appearance[5]. In the United States, the incidence of cystine stones has been reported to be 1 per cent - 3 per cent[6] in the general population and in children, the incidence is 6 per cent[7].

Of more than 7,000 urinary stone cases seen at Ramathibodi Hospital, Bangkok, Thailand, only six cases with cystine stones (< 0.06%) were detected, three were in the same family. There have been no previously reported cases elsewhere in Thailand. These cases should alert us to the possibility of cystine stones among urolithiasis patients.

Case 1

A 35 year-old Thai female living in Bangkok (HN 205-02-29), was found to have a semiopaque staghorn calculus in a congenital right single kidney. When she was 8 years old, she had a bladder stone removed. There was no history of urinary tract stone disease in the family.

The stone was first treated by the EDAP LT01 Lithotriptor in 1989. It was not broken but the pain subsided. One year later she developed hydronephrosis with flank pain and was treated as urate stone (blood uric acid was 4 mg%) with DJ stent placement and extracorporeal shockwave lithotripsy (ESWL). Fragmentation with several sessions of ESWL was unsuccessful. The stone was removed by percutaneous nephro-lithotomy (PCNL) using a Lithoclast lithotriptor, the pneumatic ballistic machine. Stone analysis by infrared spectroscopy showed pure cystine stone graphic curve (Fig. 1). The diagnosis of homozygous cystinuria was confirmed by a positive sodium cyanide (NaCN)-nitroprusside test and urinary cystine level was found by the spectrophotometry method to be 889.88 mg/day (Fig. 2). The levels of other urinary dibasic aminoacids were higher than normal, following high-performance liquid chromatography (HPLC) test (Table 1). Although microscopic urine analysis showed no hexagonal cystine crystals, the special crystal induction technique* showed formation of typical cystine crystals (Fig. 3). The diagnosis of cystine stone was delayed by 11 years, after 31 sessions of ESWL and 9 sessions of intermittent DJ stent placement in the ureter, each for 1-4 months, were performed.

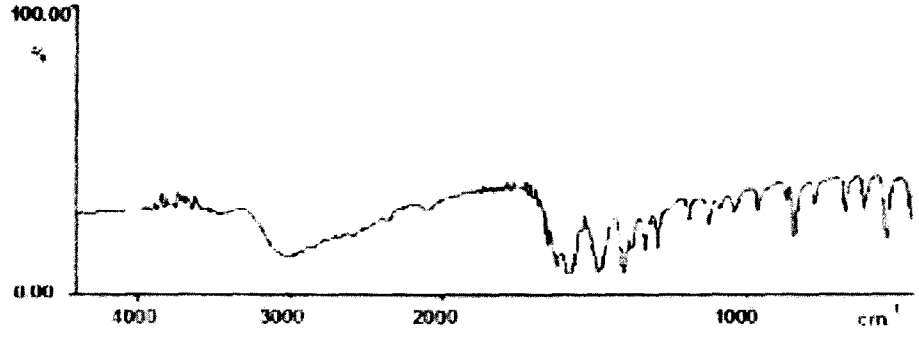

Fig. 1. Infrared spectroscopy analysis of a cystine stone shows the typical graphic curve of pure cystine stone with the same amplitude, wavenumbers (cm^{-1}) and pattern as the standard control curve.

* Crystal induction technique will be reported in other papers.

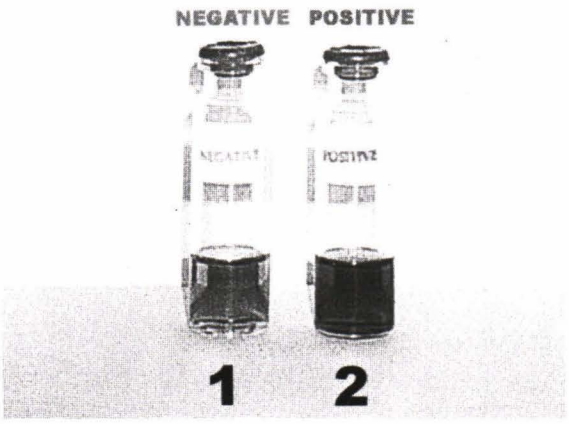

Fig. 2. **Urinary sodium cyanide (NaCN)- nitroprusside test is a qualitative test for cystinuria. The positive result, in bottle 2, was unstable brownish red compared with the normal pale yellow urine of the control (bottle 1).**

Fig. 3. **Light microscopic finding from fresh urine of the cystinuria following routine laboratory urinary analysis shows two clumps of decaying unstable cystine crystals.**

Table 1. **High-performance liquid chromatography (HPLC) test is a quantitative test for cystine. The Table shows higher levels of urinary dibasic amino acids (COLA) concentration in cystinuria than the control.**

Urinary dibasic amino acids	Concentration (umol/mmol)	Normal Control (umol/mmol)
Cystine	202	(0-10)
Ornithine	252	(0-15)
Lysine	947	(0-50)
Arginine	236	(0-20)

Post-operatively, her urine pH was kept between 7.0-7.5 by Uralyte-U®. Owing to the side effects of D-penicillamine, she was given Thiola® (alpha-mercaptopropionyl glycine-MPG). She was advised to drink 2-3 liters of water daily. At her latest follow-up, two years from the last surgical treatment she had a recurrence of two small calculi which were being treated conservatively.

Cases 2 and 3

A 45 year-old Thai male living in Sing-buri (HN 334-76-42) presented with a recurrence of right semiopaque staghorn calculus, gouty arthritis and hypertension. He had had a history of left renal stone for 20 years and had been treated in local hospitals. Apart from his younger sister, no other members of the family developed cystine stone. One year before admission his urine examination found cystine crystals. He had a staghorn calculus removal by Anatrophic nephrolithotomy one year later. By infrared spectroscopy, the stone was found to consist only of cystine. Laboratory work up showed positive urinary NaCN-nitroprusside test, several hexagonal cystine crystals seen on urinary microscopic examination, a high level of urinary cystine, ornithine, lysine and arginine (COLA). The post-operative treatment was similar to case 1, except that D-penicillamine was given at a dosage of 1.5 g per day.

The younger sister, 40 years old (HN. 317-48-14) presented with right flank pain and microscopic hematuria. She had been operated on for renal calculi twice. IVP and Ultrasound revealed two recurrent calculi a 1 cm right ureteric stone and 1.5 cm in the upper calices with hydronephrosis. The diagnosis of urinary cystine stone was derived from urinary examination by the crystal induction technique. The ureteric stone was completely removed by Ureterorenoscopy with a Lithoclast lithotriptor. After failure to remove it by PCNL, the caliceal stone was disintegrated four times by ESWL. Post-operative chemolysis was similar to her brother. At two years follow-up both siblings showed no recurrent stones.

Case 4 and 5

Unfortunately the authors could not document the hospital numbers of these two patients. These cystine crystals were found during a study of the crystallization process by Scanning Electron Microscopy between 1976-1977 (Fig. 4).

The fourth case was a male aged 37 with multiple round semiopaque stones in the right kidney who had nephrolithotomy to remove the stones. The fifth case was a female aged 42 with a large staghorn calculus in the left kidney. She had several unsuccessful ESWL sessions and consequently had PCNL to remove the stone.

As in cases 1, 2 and 3, all other tests for cystinuria were positive. Pieces of stones submitted for EM scanning showed orderly and compact arrangements of the hexagonal crystals (Fig. 5). In both these cases after more than 10 years, while on strict postoperative regimens as mentioned in cases 1, 2 and 3, these two patients had no recurrence of stones.

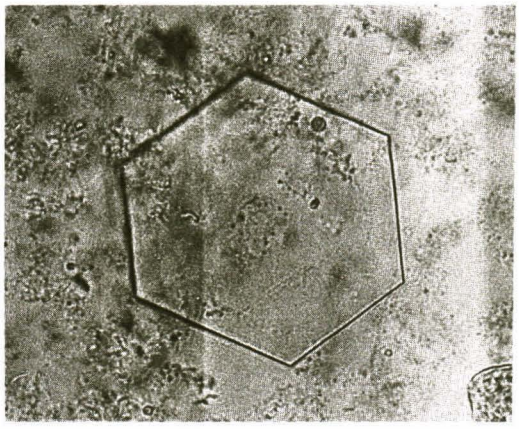

Fig. 4. Light microscopic finding from the same urine as Fig. 3. following crystal induction technique shows a complete, stable transparent hexagonal benzene ring shaped cystine crystal.

Fig. 5. A scanning electronmicroscopy of a cystine stone shows typical orderly and compact arrangements in multiple layers of the hexagonal crystals.

DISCUSSION

Wollaston, in 1816, first described the "cystic oxide" vesical calculi[8], and Civiale, in 1832, suggested the renal origin of cystine[9], cystinuria has been known as a cause of urinary calculi. The landmark papers of Dent and Rose, in 1951, elucidated clearly the deficiency of the transport system in the kidneys of patients with cystinuria[10]. Milne et al, in 1960, showed that intestinal absorption of the dibasic amino acids, cystine, ornithine, lysine and arginine (COLA), was also impaired, leaving a large amount to be destroyed by the gut flora. This gives rise to the type I, II and III cystinuria[11]. However, only the homozygous type of cystinurics type I, II or III gives rise to high urinary cystine level (> 300 mg/day) thus causing cystine lithiasis.

The striking feature of the four of five reported cases of cystine lithiasis was that all were diagnosed post-operatively by infrared spectroscopy analysis[12,13], NaCN-nitroprusside test[14], urine microscopy, and determination of daily dibasic amino-acids by amino acid analyzer, the high-performance liquid chromatography (HPLC) method[14,15].

Obviously, basic NaCN-nitroprusside test can easily diagnose the disease. With urinary cystine excretion of more than 75 mg/liter, a brown colour forms in the urine, denoting cystinuria. Microscopy of the urine will often show hexagonal cystine crystals, however the crystals are rarely found in fresh urine specimens because of instability in room temperature. In short, theoretically the diagnosis of cystinuria

should precede treatment. That is, all patients with urinary stones should have a NaCN-nitroprusside test and careful microscopic urine examination.

However, with the rarity of these cases in Thailand, those in the high risk or highly suspicious group, that is younger age, recurrent cases and resisting ESWL, should have these tests. The NaCN-nitroprusside test is not available in most laboratories and needs a sophisticated setup, thus, careful meticulous microscopic urine examination with the crystal induction technique may be more applicable for Thailand.

Pre-treatment diagnosis of cystinurics will help in planning the therapy[16]. Basicly, the treatment consists of a low protein diet, especially of methionine and glutamine, alkalinization of the urine to pH > 7.5, increased fluid intake in order to facilitate a urine output to 3-4 liters a day, and the administration of D-penicillamine or Thiola® to form disulphide complex with cystine, thus lowering the urinary cystine level to less than 200 mg/liter. If medical therapy fails, surgical or PCNL may have to be resorted to[17,18].

It might be added here that a cystine stone is compact (Fig. 5) and often resists fragmentation by ESWL[19]. However, it should be borne in mind that two-third of cystinurics form pure cystine stones while the remaining one-third form calcium oxalate, calcium phosphate or urate calculi. For the latter one-third, ESWL may be effective.

SUMMARY

Even though urinary cystine stones are very rare in Thailand, the authors were able to identify them by several methods during the pre-operative and post-operative period. Without definite diagnosis, the treatment and prevention of cystine stone might be unsuccessful, thus, wasting much time, effort and expense of patients and physicians.

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รายงานผู้ป่วยห้ารายโรคนิ่วซีสตีนในทางเดินปัสสาวะในประเทศไทย

สุชาติ ไชยเมืองราช, พบ, กมลกานต์ ชมะวรรณ, คบ**, จินตนา โมกขะเวส, คม**, ชูชาติ หิมวิภาค, วทบ**, นฤมล จันทร์วิเมลือง, วทบ**, วาสนา สถิตย์จันทรากุล, วทม***, วชิร คชการ, พบ*, ไพฑูรย์ คชเสนีย์, พบ**

นิ่วซีสตีน เป็นโรคนิ่วทางเดินปัสสาวะที่เกิดทางพันธุกรรม เกิดเป็นขึ้นใหม่ได้บ่อย และไม่สามารถรักษาได้ด้วยเครื่องสลายนิ่ว พบได้ยากในประเทศไทยไม่มีผู้รายงานมาก่อน รายงานผู้ป่วยห้าราย จากโรงพยาบาลรามาธิบดี สองรายเป็นพี่น้องกัน ตรวจพบหลังการผ่าตัด ด้วยวิธีต่าง ๆ คือ ตรวจก้อนนิ่วทุกก้อนโดยใช้เครื่องวิเคราะห์นิ่วอินฟาเรด สเปกโตสโคปี, ตรวจจากน้ำปัสสาวะเพื่อหาซีสตีน โดยวิธีโซเดียมไซยาไนด์ไนโตรปรัสซาย และปริมาณของซีสตีนโดยสเปกโตรโฟโตเมตรี, ตรวจจากน้ำปัสสาวะ หาผลึกซีสตีนด้วยกล้องจุลทรรศน์สแกนนิ่งอีเลคตรอน และนอกจากนี้ยังตรวจพบไดเบสิคแอมมิโนแอซิดสามตัวที่ออกมาจำนวนมาก ในน้ำปัสสาวะที่เป็นเฉพาะกับโรคนี้ คือ ออนิทีน, ไลซีนและอากินีน โดยวิธี เฮชพีแอลซี สองรายสุดท้ายเป็นผู้ป่วยที่พบจากการใช้เครื่องอินฟาเรด สเปกโตสโคปี และกล้องสแกนนิ่งอีเลคตรอนไมโครสโคปปี ทั้งนี้ได้กล่าวถึงลักษณะทางธรรมชาติวิทยา, การตรวจพบทางคลินิก, การวินิจฉัยโรค, วิธีการรักษาและการป้องกันโรคนี้โดยละเอียด

คำสำคัญ : นิ่วซีสตีน, ผลึก, ซีตีนในปัสสาวะ, อินฟาเรด สเปกโตสโคปี, โซเดียมไซยาไนด์ไนโตรปรัสซาย, สเปกโตรโฟโตเมตรี, กล้องจุลทรรศน์สแกนนิ่งอีเลคตรอน, ไดเบสิคแอมมิโนแอซิด, เครื่องสลายนิ่ว

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