CASE REPORT
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Xanthine Stones in an Infant: A Case Report and Clinical Insights

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Abstract

Xanthinuria is a rare autosomal recessive condition characterised by increased urinary xanthine excretion resulting from a derangement in purine metabolism, accounting for only 0.1% of pediatric stones. Incidence of inherited xanthinuria lies in the range of 1:6,000 to 1:69,000. A male baby in the latter part of infancy presented with a history of recurrent episodes of abdominal pain, fever, vomiting for 4 months, and a recent history of passage of calculi. On evaluation, radiolucent calculi were noted in the left renal pelvis and in the bilateral distal ureters, causing hydroureteronephrosis. During initial cystoscopy, a posterior urethral valve was incidentally noted and fulgurated. Ureteroscopic lithotripsy in two sessions cleared the stone burden. Crystallographic analysis of the stone was suggestive of a xanthine stone. Selective genetic analysis for *XDH1* gene targeting exons 6F, 8F, 10F, 16F, 21F, 23F, was done on samples from the index case, first and second degree relatives. Interestingly, no mutations were recorded in the index case, but a mutation was noted in one first-degree relative and one second-degree relative, respectively, in exons 21F [c. 2211C>T (p. I737I)] and 8F [g. 682G>C (p. T202T)]. As only targeted gene analysis was done, the possibility of mutations in other exons of the *XDH1* gene cannot be ruled out. A complete metabolic workup along with stone analysis helps in the early diagnosis of metabolic conditions like xanthinuria, which can be further confirmed with genetic studies. Diet and lifestyle changes can help in preventing recurrence of stones and avoiding further renal damage.

Keywords: Endourology, general urology, pediatric urology

Introduction

Radiolucent calculi in children represent 5-10% of kidney stones in developed countries and 27% of pediatric urolithiasis in underdeveloped countries. The majority of these cases are uric acid stones followed by xanthine stones and 2,8-dihydroxyadenine stones (1). Xanthinuria is a rare autosomal recessive condition characterised by increased urinary xanthine excretion resulting from a derangement in the purine metabolism. Essentially, the last two steps of purine degradation involving the conversion of hypoxanthine to xanthine, and xanthine to uric acid are affected. This results in increased accumulation of hypoxanthine and xanthine and their subsequent excretion in the urine. Three forms of xanthinuria have been described based on distinct mutation loci: type I (xanthine dehydrogenase/oxidase deficiency), and type II (xanthine dehydrogenase and aldehyde oxidase deficiency) are collectively referred to as "classical xanthinuria". A third clinical type, associated with molybdenum cofactor deficiency (deficiency of sulfite oxidase and aldehyde oxidase), has also been described (2). Xanthinuria is a rare cause of urolithiasis in children, accounting for about 0.1% of pediatric stones (3). It is estimated that the incidence of xanthinuria, which is inherited, lies in the range of 1:6.000 and 1:69.000 (4). Common presentation in the pediatric age group is abdominal pain (44%), hematuria (38%), fever (15%), and other urinary tract infection associated symptoms (5).

Apart from the patients with hereditary xanthinuria, another group of individuals who are frequently affected by xanthine stones is patients with Lesch-Nyhan syndrome, on allopurinol therapy. Lesch-Nyhan syndrome causes developmental delay in children. These children may find it difficult to express their symptoms, resulting in a delay in diagnosis. Hence, imaging becomes extremely important in these patients. As xanthine urolithiasis tends to recur in the majority of the cases, these

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patients need to undergo multiple imaging studies throughout their lifetime (6).

Another rare cause of calculi in the pediatric population is cystinuria. About 6% of all pediatric urolithiasis is due to cystine. Cystinuria is an autosomal recessive disorder resulting in decreased reabsorption of cystine and other dibasic amino acids like ornithine, lysine, and arginine. However, these stones are radiopaque and may be identified on an X-ray (7).

Case Presentation

A male baby in later infancy born out of a third-degree consanguineous marriage presented with a history of recurrent episodes of abdominal pain, fever, vomiting and crying during micturition on and off for the past 4 months. There was a history of passage of 2 tiny calculi one week back (Figure 1A) associated with mild hematuria, following which the infant was referred to the urologist. The antenatal and post-natal periods were uneventful. The appropriate age-related developmental milestones were attained. The baby was being breastfed, and weaning had been started with a home-based cereal diet. Abdominal examination did not reveal any significant findings. Written informed consent for publication of the case details, including history, investigation reports, and other relevant information was obtained from the infant's parents.

The investigations revealed hemoglobin 9.7 mg%, mild leucocytosis (14,600 cells/cumm), serum creatinine (0.74 mg/dL), calcium 10.9 mg/dL, uric acid- 2.0 mg/dL (normal range 3-6 mg/dL) and vitamin D- 26.69 ng/mL (ref range 6.2-53.2 ng/mL). Urinalysis showed 10-15 pus cells and 8-10 red blood cells. Urinary pH- 6.5, calcium- 31.65 mg%, creatinine- 43.6 mg% and urine calcium creatinine ratio- 0.72 were in the normal range. Urine culture was sterile.

Ultrasonography showed bilateral 6 mm calculi in renal pelvis with grade I hydronephrosis. The X-ray of the kidney ureter bladder region (Figure 1B) did not show any radio-opaque shadow. Two days later the baby underwent a computed tomography (CT) abdomen (Figure 1C) which revealed 6.5 mm [402 Hounsfield unit (HU)] right distal ureter calculus just proximal to ureterovesical junction (UVJ) causing mild right hydroureteronephrosis (HUN), a 6 mm obstructive calculus (352HU) in left UVJ causing mild left HUN and a 10 mm (427 HU) non obstructive calculus in left renal Pelvis.

Differential diagnosis-CT scan ruled out any gross anatomic abnormality, and a metabolic workup was done considering the possibility of hypercalciuria, hyperoxaluria, hypocitraturia, cystinuria, hyperuricosuria, and Xanthinuria as potential causes of urolithiasis in this infant.

Treatment

The baby was scheduled for bilateral ureteroscopic lithotripsy (URSL) using a 4.5 Fr ureteroscope with a thulium fiber laser. During this procedure, both the lower ureter calculi were fragmented, and bilateral Double J stenting was done. Two weeks later, the baby underwent a second procedure, specifically, a left URSL for the 10 mm calculus in the left renal pelvis. The stone fragments were sent for crystallographic analysis (Figure 2A), which was suggestive of compact masses of rhombic crystals indicative of xanthine stones (xanthine 71%).

In view of the limited resources and available testing facilities, we did a targeted genetic analysis of the child and family members (parents and grandmother) to identify mutations in the *XDH1* gene, focusing on exons 6F, 8F, 10F, 16F, 21F, 23F, as these are the frequently reported mutation sites. Interestingly, no mutations were recorded in the index case, but a heterozygous mutation

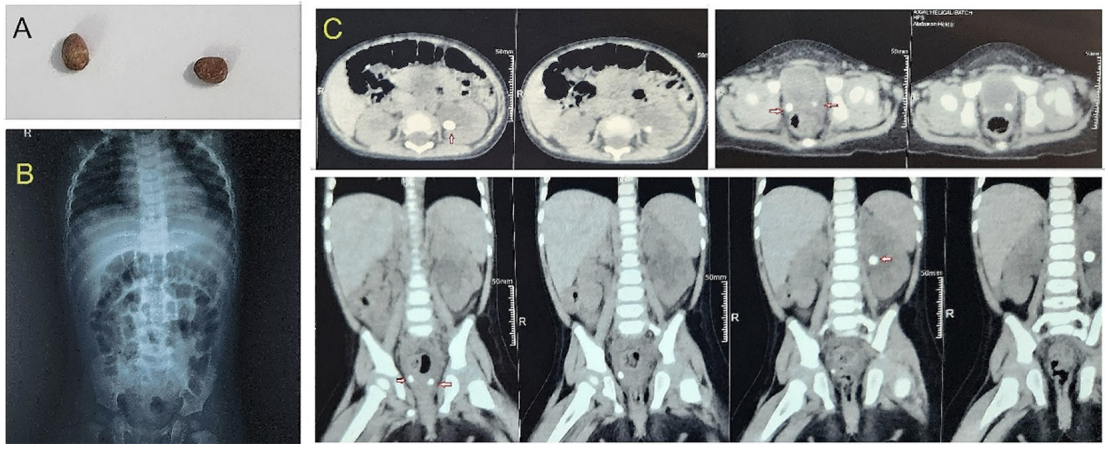

Figure 1. A. Two tiny calculi passed spontaneously. B. X-ray of the KUB region showing no evidence of any radio-opaque shadow. C. Axial and coronal CT images showing the 10 mm (427 HU) non obstructive calculus in left renal Pelvis, a 6.5 mm (402 HU) right distal ureter calculus, 6mm calculus (352 HU) at left UVJ (Calculi are Indicated by red arrows)

KUB: Kidney ureter bladder, CT: Computed tomography, HU: Hounsfield unit, UVJ: Ureterovesical junction

was noted in one first-degree relative (Father) and one second-degree relative (Grandmother) in exons 21F [c. 2211C>T (p. I737I)] and 8F [g. 682G>C (p. T202T)], respectively (Figure 2B, C). the relatives were asymptomatic and had no history of urolithiasis. Thus, a conclusion may be drawn that there may be mutation in one of the remaining 30 exons that were not analysed.

Complete clearance of the ureteric and renal pelvic stones was achieved. The parents were counselled to administer a low purine diet to the baby along with an alkalizer and to maintain adequate hydration. On being followed up for 6 months after the procedure, the baby was doing well and had no recurrence of abdominal pain and urolithiasis. A follow-up CT scan did not show any evidence of residual or new calculi.

Discussion

Hereditary xanthinuria is an uncommon condition that alters purine metabolism, leading to urolithiasis. As a result, these individuals can develop renal stones at any age, including infancy.xanthine stones or any urolithiasis in children should receive special attention, as they are associated with significant morbidity due to the propensity of the renal stones to recur (8,9).

The peculiar property of xanthine stones is their radiolucency, making it difficult to detect them on plain radiographs. The physical appearance of the calculus is round and brownish in color. They may be composed of pure xanthine or may contain a certain proportion of hypoxanthine. The urinary pH is a major factor affecting the solubility of oxypurines. The urinary supersaturation of oxypurines at acidic pH leads to precipitation and stone formation. The other differential diagnosis for radiolucent stones is uric acid stones. However, these are associated with hyperuricosuria (10,11). In our patient, the urine was also slightly acidic, and the stones were radiolucent and not evident on X-ray. Ultrasound helped in detecting the stones. CT gave the exact size and location of stones, which had a low density in the range of 400 HU, and helped in planning the management.

In humans, the activity of xanthine oxidase/xanthine dehydrogenase is predominant in the liver and small intestine. Hence, the conventional method to establish hereditary xanthinuria is by an allopurinol loading test or a liver biopsy. In the current context, the approach to diagnose the type of xanthinuria may be broadly divided into a three-step algorithm as shown below (Table 1) (12).

Establishing the diagnosis and characterising the exact phenotype (type I or II), based on clinical and biochemical tests alone, is difficult, thereby necessitating the use of molecular testing. Clinical tests include stone analysis, demonstration of an elevated urinary xanthine or hypoxanthine excretion, and measurement of XDH/xanthine oxidase activity in liver or intestinal biopsy samples (13). Biochemical tests to detect xanthinuria include estimating the level of uric acid in the blood, which is usually very low (below 2 mg/dL). Measurement of urinary xanthine and hypoxanthine requires high performance liquid chromatography and the normal 24-hour urine values are below 40 mol/L and 70 mol/L, respectively (14). In the current

Table 1. Approach to diagnose the type of xanthinuria

Laboratory tests	Urinary metabolites	Genetic studies
Extremely low level of serum/urinary uric acid	N1-methyl-2-pyridone-5-carboxamide	Molecular genetics
Stone composition analysis	N1-methyl-4-pyridone-5-carboxamide	
	These products are results of the oxidation of N1-methylnicotinamide by aldehyde oxidase	

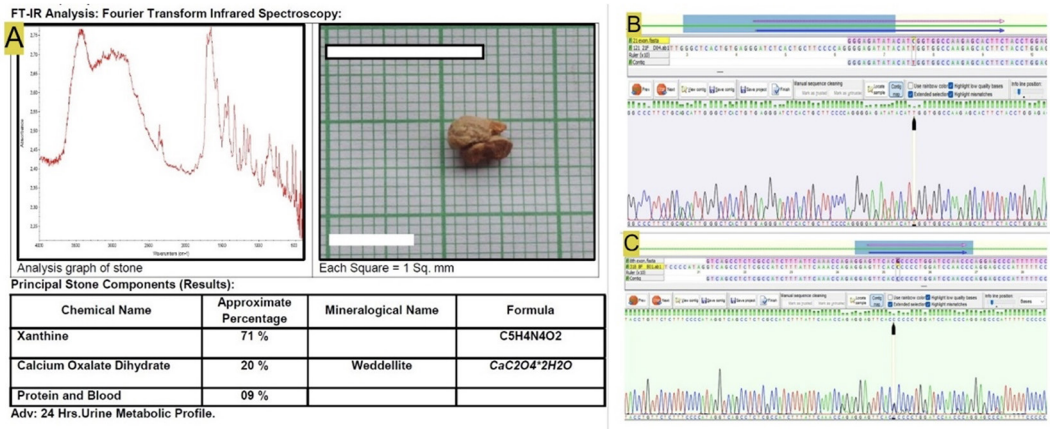

Figure 2. A. Stone analysis by FT-IR showing xanthine (71%) as the principal component. B. Heterozygous mutation in exon 21F [c. 2211C>T (p. I737I)] noted in first degree relative. C. Heterozygous mutation in exon 8F [g. 682G>C (p. T202T)] noted in second degree relative

FT-IR: Fourier transform-infrared spectroscopy

case, we observed that the serum uric acid levels were low, which was in line with our diagnosis of xanthinuria. Urinary xanthine and hypoxanthine levels were not estimated due to the unavailability of liquid chromatography.

The human *XDH* gene is located on chromosome 2p23.1. The *XDH* gene has 36 exons, which code for a 1.333 amino acid protein. Currently, there are about 18 mutations in the XDH coding region: 16 missense/non-sense, one small deletion, and one small insertion. Out of these mutations, 7 mutations are known to cause clinical xanthinuria (2,15). In our case, we performed genetic analysis using primers targeting a few specific coding regions (exons 6F, 8F, 10F, 16F, 21F, 23F) which are known to cause clinical xanthinuria. However, no mutation was detected in the index case, indicating that the mutation may be present in one of the remaining coding regions.

Most of the individuals with heterozygous mutations in the *XDH* gene do not demonstrate hypouricemia or symptoms of urolithiasis. In some rare instances, their urinary oxypurine excretion may increase and lead to stone formation. However, the incidence of urolithiasis in heterozygotes has not been estimated reliably (16). In the current family, too, we could identify a first-degree and a second-degree relative with heterozygous mutation in exon 21F and 8F, respectively, and both had no history suggestive of urolithiasis.

In the present case, we were able to achieve stone clearance with URSL alone. Other modalities for management of these calculi include Micro PCNL and retrograde intrarenal surgery. Shockwave lithotripsy can be used in the treatment of these stones but comes with the associated disadvantages of multiple sittings and need for general anaesthesia in pediatric patients (17,18).

Management of xanthinuria is primarily aimed at avoiding recurrence of stones and the subsequent complications. A strictly low purine diet (avoidance of seafood, alcohol, cheese, and chocolates) must be advised, along with adequate hydration, Alkalisers are commonly prescribed because the solubility of oxypurines is pH dependent. Excessive physical activity may cause renal or intramuscular deposition of xanthine crystals and hence must be avoided (19).

The best way to prevent recurrent urolithiasis in patients with xanthinuria is a low purine diet and an adequate intake of fluids, as per the current literature. However, there is ongoing research to identify new agents that can prevent the crystallisation of xanthine in the urine of recurrent xanthine stone formers. Grases et al. (20), in their *in vitro* studies, identified two metabolites of theobromine-7-methylxanthine and 3-methylxanthine, which can prevent crystallisation of xanthine. However, further clinical trials are necessary to establish the *in vivo* efficacy of theobromine metabolites in preventing xanthine nephrolithiasis (20).

Conclusion

Any pediatric patient presenting with urolithiasis must undergo complete metabolic evaluation. A stone analysis will further aid in diagnosis of certain rare conditions, like xanthinuria, which can be confirmed by genetic studies. In patients with xanthinuria, simple diet restrictions with lifestyle changes will help prevent the recurrence of stones and avoid further renal damage.

Ethics

Informed Consent: Written informed consent for publication of the case details, including history, investigation reports, and other relevant information was obtained from the infant's parents.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.B.P., S.P., B.S.P., M.K.V., Concept: S.B.P., V.S.K., S.P., B.S.P., G.S.K., Design: S.B.P., V.S.K., M.K.V., Data Collection or Processing: B.S.P., G.S.K., Analysis or Interpretation: S.B.P., M.K.V., G.S.K., Literature Search: V.S.K., B.S.P., M.K.V., G.S.K., Writing: V.S.K., S.P., M.K.V.

Conflict of Interest: No conflict of interest was declared by the authors.

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