Case Report

Giant Bladder Calculi: A Rare Cystinuria-Associated Nephrolithiasis in Rural Pediatrics

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ABSTRACT

Background: Pediatric giant bladder calculi (vesicolithiasis) are uncommon and rare. It is more frequently reported in adolescents. In the pediatric population, predisposing factors differ from those in adults and typically include urinary stasis secondary to obstruction, congenital anomalies of the kidney and urinary tract (CAKUT), recurrent urinary tract infections, dehydration, and malnutrition. Metabolic abnormalities are often underdiagnosed, particularly in rural and suburban settings. The diagnosis of metabolic urolithiasis in rural pediatric practice remains challenging due to multiple factors, including low clinical suspicion and awareness, limited availability of specialized metabolic investigations, lack of local stone composition and genetic analyses, restricted access to pediatric subspecialists, and prolonged referral pathways that delay diagnostic results. Additional barriers, such as difficulties in obtaining 24-hour urine collections, socioeconomic constraints, and limited awareness of inherited stone disorders, may further contribute to delayed diagnosis

Aims: To describe an unusually early presentation of cystinuria-associated giant bladder calculi and highlight diagnostic challenges in a rural pediatric setting.

Case Description: A 2-year-2-month-old girl presented with lower abdominal pain and oliguria, with a one-year history of recurrent abdominal pain. Imaging demonstrated large bladder calculi with right ureteric and renal calculi. Vesicolithotripsy removed two bladder stones; stone composition analysis was unavailable. Subsequent metabolic evaluation was delayed by approximately nine months. A 24-hour urine amino acid analysis showed markedly elevated cystine excretion of 669.02 mmol/mol creatinine (reference <50), with normal homocysteine, supporting cystinuria as the underlying metabolic disorder. Renal function remained preserved and no recurrent stone formation was identified on follow-up imaging.

Conclusion: Early-onset, recurrent, large, or atypically located urinary stones in children should prompt metabolic evaluation. In resource-limited settings, timely biochemical testing, stone analysis where available, specialist referral, and long-term preventive management are important to reduce recurrence and preserve renal function. These challenges highlight the need for greater awareness, improved access to diagnostics services, and strengthened referral networks to facilitate the early identification and management of children with metabolic stone disease. Here, we report a case of giant bladder calculi presenting in early childhood and underscore the rare underlying aetiology : Cystinuria.

Keywords: Giant bladder calculi; Renal calculi; Metabolic stone disease; Vesicolithiasis; Cystinuria; Pediatrics; Rural.

INTRODUCTION

Nowadays, pediatric vesicolithiasis is uncommon in children and account for only a small proportion of urinary tract calculi; however, the number of affected children has shown a gradual increase over the recent years,[1,2] likely due to changes in lifestyle and dietary habits, as well as improved accessibility to radiological imaging modalities.[3,4]

Unlike adults, bladder stones in children frequently warrant investigation. It is commonly associated with constipation and urinary tract infections due to urinary stasis. Although constipation and urinary tract infection are common associations, CAKUT, urogenital abnormalities, as well as inherited metabolic disorders and environmental factors should be thoroughly investigated to identify potential underlying causes.[4-6]

Approximately 75% of urinary calculi originate in the kidneys before migrating to other parts of the urinary tract.[6] Although less common, bladder stones account for approximately 0.3 - 5% of all urinary tract calculi,[3] and may either form primarily within the bladder or descend from the upper urinary tract.

The clinical presentation of urinary stone disease in children differs from that in adult. In younger children, symptoms are often vague and non-specific, including irritability, vomiting, and inconsolable crying. [7] Furthermore, some children may present with minimal symptoms or remain asymptomatic.[8]

Most urinary stones are composed of calcium, cystine, struvite, and uric acid.[9] Although cystine stones are uncommon in adults, accounting for only 1–2% of urinary tract stones, they are more frequently encountered in children, where they may represent up to 10% of urolithiasis cases.[10] In contrast, Sreenevasan G. reported that cystine stone was about 0.5% of all stone analyses in Malaysia.[1] Metabolic causes of urolithiasis are often underdiagnosed due to diagnostic challenges, with cystinuria being the most common inherited metabolic disorder associated with urinary stone formation.[11]

Cystinuria is a rare autosomal recessive metabolic disorder and genetic defect caused by mutations in the *SLC3A1* or *SLC7A9* genes,[12,13] resulting in defective proximal renal tubular reabsorption of cystine and other dibasic amino acids, leading to accumulation of the amino acids cysteine and subsequent stone formation.[7,14] Although cystine stones account for only 1-2% of urinary stones in adults, they accounts for approximately 6–8% of all pediatric urolithiasis cases, with a prevalence of 1-5 per 10,000 individuals and remain the most common inherited metabolic cause of urinary calculi. In Malaysia, cystine stones account for only approximately 0.5% of analyzed urinary stones. Stone formation affects all age groups, although the onset typically occurred between 10 and 30 years of age, most commonly in adolescence, and is more frequently reported in males than female.[10,13] Although cystinuria has been reported as early as the neonatal period and even at birth,[15] presentation during infancy or early childhood is uncommon, making the diagnosis particularly challenging. Owing to its high recurrence rate, delayed diagnosis may result in repeated surgical interventions and progressive renal impairment.[12,16] Furthermore, cystinuria is associated with a high prevalence of chronic kidney disease (CKD).[12] In this report, we report a case of 2-year-2-month-old girl with giant bladder calculi secondary to cystinuria, representing the youngest reported case of cystinuria-associated giant bladder calculi in Malaysia. This case highlights the importance of considering inherited metabolic disorders in young children representing with bladder stones and underscores the value of early metabolic evaluation to prevent recurrent stone disease and preserve long-term renal function.

Aims

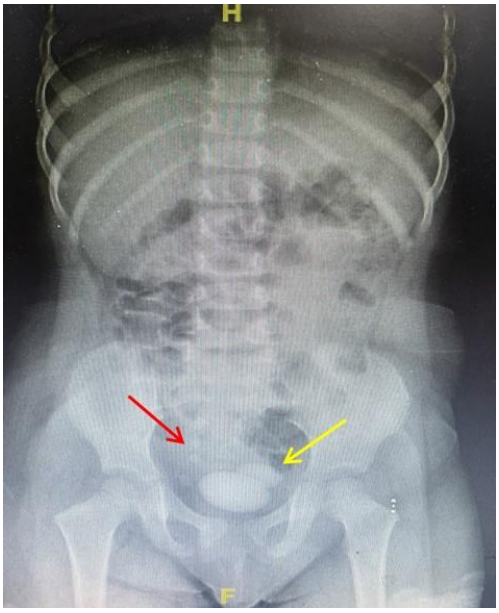
To describe an unusually early case of cystinuria-associated giant bladder calculi in a 2-year-2-month-old girl, highlighting the diagnostic challenges, emphasize the importance of metabolic evaluation in pediatric urolithiasis, and the importance of early metabolic evaluation and long-term recurrence prevention, particularly in rural healthcare settings.

Case Description

A 2-year-2-month-old girl, born to a non-consanguineous Malay parents, presented with a 2-day history of acute lower abdominal pain and oliguria. Her antenatal, perinatal, infancy, and medication histories were unremarkable. There was no family history of renal disease or urolithiasis. Her growth and development milestones were normal. She had experienced recurrent, self-limiting episodes of abdominal pain over the preceding year. Her mother denied any history of dysuria, urgency, hesitancy, haematuria, straining during urination, or constipation.

On physical examination revealed unremarkable with her weight was 13.3 kg (75th to 90th percentile), height was 84 cm (75th to 90th percentile), and head circumference was 48 cm (15th to 50th percentile). She had no facial dysmorphic features. At presentation, her pain score ranged 2 to 6 out of 10. Otherwise, she was haemodynamically stable and afebrile but had marked suprapubic tenderness on abdominal examination. There was no hepatosplenomegaly, palpable faecal mass was felt and a negative renal punch. No neuromuscular abnormalities were identified.

Figure 1. KUB radiograph showing bladder calculi (yellow arrow) and multiple right ureteric calculi (red arrows).



Baseline investigations, including haematological parameters, renal profile, serum electrolytes, and inflammatory markers were within normal limits including calcium and uric acid. Urine full examination and microscopic examination (UFEME) demonstrated significant pyuria with the presence of leucocyte (3+) (250-500

leucocytes/microliter), microscopic haematuria with erythrocyte (1+) (5-10 erythrocytes/microliter), and positive nitrite. No casts or crystals were observed, and urine culture yielded no bacterial growth. Urine electrolytes analysis was performed and demonstrated normal urinary excretion levels of calcium, magnesium, and inorganic phosphate.

Abdominal radiograph and ultrasonography revealed large bladder calculi and multiple right ureteric calculi (Fig. 1) with a right kidney calculus. She was treated empirically for a urinary tract infection with broad-spectrum parenteral antibiotic coverage and concomitant nephrolithiasis. Subsequently, she was referred to the paediatric surgery and urology team for further evaluation and management.

Vesicolithotripsy was successfully performed, resulting in the removal of two bladder stones. However, stone composition analysis was not performed. Following the procedure, the patient remained asymptomatic after completing the course of antibiotic. Subsequent follow-up demonstrated preserved renal function, normal urinalysis findings, with no evidence of recurrent stone formation on subsequent imaging (Fig. 2). The family was counselled on the importance of strict adherence to both pharmacological and non-pharmacological management strategies.

Figure 2. Follow-up KUB radiograph showing resolution of the calculi following medical and surgical intervention.



Given the exceptionally young infant presentation and the rarity of giant bladder calculi in children, an extensive additional investigation, including comprehensive metabolic evaluation, were undertaken during follow-up, to identify an underlying metabolic disorder. The inborn errors of metabolism (IEM) screening profile were non-diagnostic. However, urinary cystine level was markedly elevated while homocystine level remained within the normal range, confirming the diagnosis of cystinuria. 24-hour urine amino acid analysis demonstrated markedly elevated urinary cystine excretion of 669.02 mmol/mol creatinine (reference range: <50 mmol/mol creatinine), approximately 13 times the upper limit of normal. In contrast, urinary homocystine excretion level was within the normal range at 1.54 mmol/mol creatinine (reference range: <4.5 mmol/mol creatinine) (Table 1). These findings

established cystinuria as the underlying metabolic disorder responsible for the patient's bladder calculi. Notably, the definitive metabolic diagnosis was established approximately nine months after the initial presentation.

Table 1. Result of 24-hour urine for Cystine and Homocystine test

Test	Result (mmol/mol creatinine)	Range
Cystine	**699.02**	< 50
Homocystine	1.54	< 4.5

Case Discussion

This case is clinically notable for several reasons. First, the patient presented at only 2 years and 2 months of age with giant bladder calculi, which is considerably younger than the usual age at which cystinuria is recognized clinically. Second, the presentation was dominated by giant bladder calculi rather than the more typical recurrent renal or ureteric stones. Bladder stones are less common in children than in adults.[17] Although pediatric bladder stones may be associated with dehydration, infection, nutritional factors, or urinary stasis, an early-onset or atypical presentation should prompt evaluation for inherited metabolic causes.[17-19] In pediatric population, calcium oxalate is the predominant stone composition, accounting for approximately 73% of stones, followed by calcium phosphate (9%), and struvite (13%).[18]

The rural setting contributed to the diagnostic challenge. Plain abdominal film is often the initial imaging modality used in the evaluating of urinary stone disease, as approximately 90% of urinary calculi are sufficiently radiopaque to be detected. However, ultrasonography remains an essential and safe diagnostic tool because it does not involve ionizing radiation and is useful to visualize radiolucent calculi, as well as identifying structural and functional abnormalities, and complications of obstructive uropathy, including hydronephrosis, hydroureter, pyuria, and pyonephrosis.

Thirdly, the diagnosis was established in a rural pediatric setting, where local access to specialized metabolic testing, stone composition analysis, and pediatric nephrology services was limited, and the definitive metabolic diagnosis required approximately nine months. Given the markedly elevated 24-hour urinary cystine excretion, together with normal homocystine levels and the presence of early-onset giant bladder stone disease in a child aged only 2 years and 2 months, strongly represents a confirmed cystinuria as the underlying metabolic cause rather than an isolated sporadic bladder stone. Without early recognition and appropriate management, cystinuria predisposes affected children to lifelong recurrent nephrolithiasis, ureterolithiasis, and bladder stone formation, with consequent risks of urinary obstruction, recurrent infection, and renal scarring.

Therefore, metabolic disorders such as cystinuria should be considered in the differential diagnosis of all pediatric patients presenting with urolithiasis, particularly recurrent or atypical stone disease.[19] Based on result on

biochemical findings shown on Table 1, there is strong evidence supporting the diagnosis of cystinuria. The normal homocystine level helps exclude homocystinuria as the cause of elevated sulfur-containing amino acids.

Several factors contributed to the delayed diagnosis. Similar diagnostic barriers have been described in rare diseases, including limited awareness, restricted access to specialized investigations, and prolonged referral pathways.[20-23] These included the rarity of cystinuria, limited local epidemiological data,[20] low initial clinical suspicion for inherited metabolic stone disease among healthcare professionals, coupled with the perception on unlikeliness to be encountered in routine practice, may further hinder timely diagnosis.[21] Delayed availability of specialised metabolic investigations, and healthcare access barriers commonly encountered in rural practice. As a result, patient with rare metabolic diseases frequently experience symptoms recurrence, reduced access to appropriate investigations and specialized treatment compared with patients with more common chronic illnesses.[22,23] This case therefore illustrates the importance of early metabolic evaluation and specialist referral in children with early-onset, recurrent, large, or atypically located urinary stones. In resource-limited settings, clinicians should maintain a high index of suspicion, ensure timely urine microscopy and biochemical testing, request stone analysis whenever possible, and arrange early referral to pediatric nephrology or metabolic services.

The diagnosis of underlying cystinuria can be established through family history assessment, urinalysis and urine microscopic evaluation, stone composition analysis with identification of characteristic hexagonal cystine crystals, or measurement of 24-hour urinary cystine excretion. Where feasible, stone analysis should be obtained because it can facilitate earlier aetiological diagnosis. When stone composition is unknown, a qualitative urine test for cystine should be conducted.[24] In this patient, stone composition was unavailable and no urinary crystals were observed; however, markedly elevated urinary cystine excretion with normal homocystine provided biochemical evidence supporting cystinuria.

Stone analysis using infrared spectroscopy and X-ray diffraction of stone analysis are the gold standard for confirming the diagnosis.[14] A comprehensive metabolic evaluation may require longer prolonged duration before definitive results become available, and potentially delaying the diagnosis of underlying metabolic disorders, particularly in rural and suburban health care settings. Moreover, owing to the rarity nature of cystinuria, the average interval between initial presentation and definite diagnosis has been reported to be as long as 7.8 years.[25]

Management of cystinuria is directed at complete stone clearance when required, prevention of recurrence, and preservation of renal function. Advances in removal techniques have transformed and expanded the treatment landscape options. The development of extracorporeal shock wave lithotripsy (ESWL) has transformed the management of urinary stone disease, allowing nearly 90% of urinary calculi to be treated using minimally invasive methods and significantly reducing the need for open surgery.[1] However, vesicolithotripsy is also an effective treatment option and may be preferred depending on stone characteristics, available facilities, and the expertise of the attending urologist.

Generally, hereditary renal stones are generally associated with increased risk for chronic kidney disease (CKD)

and progression to end-stage kidney disease (ESKD).[18,28] Therefore, conservative therapy follows a stepwise approach for long-term management comprising high fluid intake, dietary sodium reduction, moderation of animal-protein intake, and urinary alkalinisation.[14, 29-31]

Along with dietary changes, adequate fluid intake is another cornerstone of cystinuria management, as it promotes urinary dilution and reduces cystine precipitation. In addition to water, alkaline beverages with high bicarbonate and low sodium content, as well as citrus-based drinks, may be beneficial.[11] Fluid intake should be tailored according to age and anthropometry measurement in children, with the aim of achieving a 24-hour urine volume exceeding 2L/1.73m^2 including attention to overnight hydration by consume fluids before bedtime and upon awakening to prevent dehydration.[31] Dietary sodium restriction should be recommended for all patients as low sodium intake has been shown to decrease urinary cystine excretion in children.[29] Similarly, dietary protein intake restriction may further reduce cystine excretion.[30]

Urine pH is a key determinant of cystine solubility. Consequently, urine alkalinization, combined with dietary modification and adequate hydration, is generally effective strategy to improve cystine solubility and to reduce stone formation. Potassium citrate is generally safe and the preferred alkalinizing agent, with treatment titrated to urinary pH; The target urine pH is between 7.5-8.0.[28] Potassium citrate is considered effective first-line preferred alkalinizing agent and is commonly recommended.[32]

Optimizing bowel and bladder habits is equally important. Regular bladder emptying and maintenance of normal bowel function may help prevent urinary retention and constipation. Chronic constipation has been associated with an increased risk of urinary stone disease, particularly in obesity.[5,33] Rare inherited metabolic disorders are often linked to the presentation of kidney stones in early childhood, causing a high burden of recurrence.[17] Given the high prevalence of CKD and hypertension in patients with cystinuria, regular screening and lifelong follow-up are essential.[10] Accordingly, lifelong follow-up through pediatric nephrology and metabolic services is warranted with radiological imaging to monitor for recurrent stone disease and enable early recognition of renal complications.

If recurrent stone formation persists despite good adherence to hydration, dietary measures, and alkalinization, cystine-binding thiol drugs such as tiopronin or D-penicillamine may be considered under specialist supervision.[14,30,34] These agents increase cystine solubility but may cause significant adverse effects and therefore require clinical and laboratory monitoring. Long-term follow-up should include surveillance for recurrent stones, renal function, blood pressure, and treatment-related complications.[10,14]

Family genetic evaluation should be considered, particularly for asymptomatic siblings of patients with cystinuria,[35] to facilitate early diagnosis, intervention and proper treatment with a cystine chelating agent.[36] Although no universally accepted screening modality for urolithiasis exists, genetic counselling and screening based on molecular diagnostics, biochemical investigations, and family history assessment may facilitate the identification of genetic disorders associated with stone formation, particularly cystine and other rare urinary stones.[37]

Compared with previously published pediatric cases, the present case is notable because of the very young age at presentation and the formation of giant bladder calculi. Most reported pediatric cystinuria cases describe renal or ureteric calculi, recurrent nephrolithiasis, or diagnosis later in childhood. Bladder stone formation secondary to cystinuria in a toddler is therefore uncommon and clinically important. This case adds to the limited literature on early-onset cystinuria-associated bladder calculi and highlights the need to consider inherited metabolic disease even when bladder stones occur in settings where nutritional, infective, and dehydration-related causes are common. Earlier recognition may allow preventive therapy and structured follow-up before recurrent stone disease or renal complications develop.

Conclusion

Cystinuria should be considered in young children with early-onset, recurrent, large, or atypically located urinary stones, including bladder calculi. A prompt metabolic evaluation, stone analysis when available, and early specialist involvement can shorten diagnostic delay. Long-term management should focus on hydration, dietary measures, urinary alkalinization, escalation to cystine-binding therapy when clinically indicated, surveillance for recurrence, and preservation of renal function. However, published Malaysian data on pediatric cystinuria and cystinuria-associated bladder calculi remain limited, underscoring the importance of reporting rare cases to improve recognition, facilitate earlier diagnosis, and guide clinical management. This case also highlights the need for further Malaysian research on the epidemiology and aetiology of pediatric urolithiasis and cystinuria to improve understanding of these rare conditions. Greater awareness among healthcare professionals is essential to facilitate early recognition of inherited metabolic disorders and prompt comprehensive metabolic evaluation in children presenting with early-onset urinary stone disease. In summary, we have presented the youngest Malaysian reported case of giant bladder calculi secondary to cystinuria.

Ethics and Consent

Institutional ethical approval was obtained for publication of this case report. Written informed consent was obtained from the patient's parent for publication of the clinical details and the accompanying radiological images.

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