Case Report

Urinary stone in a 12-year-old adolescent with new-onset type 1 diabetes and diabetic ketoacidosis

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Highlights

- A 12-yr-old adolescent with new-onset T1D and DKA developed urinary stones.
- The patient had no metabolic abnormalities predisposing to urinary stone formation.
- Physicians should consider urinary stone formation in patients with DKA.

Abstract. Dehydration and acidosis increase the risk for urinary stone formation. Urinary stones have been reported in three pediatric cases of diabetic ketoacidosis (DKA). A 24-h urine collection was performed for two of the three children. One patient had high urine sodium levels, while the other had low urine citrate excretion. We report the case of a 12-yr-old adolescent boy with urinary stones, new-onset type 1 diabetes mellitus (T1D), and DKA, excluding other metabolic disorders. After DKA was diagnosed, the patient received a 0.9% saline bolus and continuous insulin infusion. Hyperglycemia and ketoacidosis were well-controlled on the third day after admission. However, the patient developed abdominal pain radiating to the back. Urinary stones were suspected, and a urinalysis was performed. The patient's urine revealed significant elevation in red blood cells and calcium oxalate crystals. Computed tomography revealed a high-density left ureteric mass, suggestive of a urinary stone. Although both the previously reported pediatric cases involved metabolic diseases, additional tests in this patient excluded metabolic diseases other than T1D. DKA may be related to the formation of calcium oxalate crystals owing to dehydration and acidosis. Therefore, physicians should consider urinary stone formation in DKA patients.

Key words: urinary stone disease, pediatric case, calcium oxalate stone, diabetic ketoacidosis

Introduction

Diabetic ketoacidosis (DKA) occurs in approximately 15–70% of patients with new-onset type 1 diabetes mellitus (T1D) (1). DKA results from a deficiency in circulating insulin levels and increased levels of counterregulatory hormones. These include catecholamines, glucagon, cortisol, and growth hormone (2). These hormones promote glycogenolysis and gluconeogenesis, leading to hyperglycemia, polyuria, and intravascular dehydration. Simultaneous lipolysis with the release and oxidation of free fatty acids facilitates gluconeogenesis, ketogenesis, and the consequent metabolic acidosis.

Reportedly, urinary stones are rarer in children (incidence, 2–3%) (3) than in adults (incidence, 5–12%) (4). Calcium oxalate and phosphate stones are the major types of urinary stones observed in both adults and children (4). Osmotic diuresis secondary to hyperglycemia causes the loss of water and electrolytes, resulting in dehydration. Varying degrees of dehydration occur in children with diabetes mellitus (1, 2). Additionally, patients with diabetes mellitus exhibit changes in urinary composition, such as increased urinary calcium and phosphate excretion, high quantities of urinary oxalate, and a low urinary pH (5–8). Dehydration, increased urinary calcium/phosphate excretion, and acidosis increase the risk of crystallization and calcium stone formation (9, 10). Considering these reports, DKA-induced severe dehydration, hyperglycemia, and acidosis may predispose patients with diabetes mellitus to urinary stone formation. However, to date, urinary stones have been reported in three pediatric DKA cases (11). A 24-h urine collection was performed for two of the three children. One patient had high urine sodium levels, and the other had low urine citrate excretion (11). Here, we report a case of urinary stone in a child with new-onset T1D and DKA, excluding other metabolic disorders.

Patient and Methods

A 12-yr-old Japanese adolescent boy was referred to Kurume University Hospital to evaluate generalized fatigue, polydipsia, and polyuria. Upon admission, the patient reported no history of urinary tract infection or abnormal urinalysis indicating the presence of occult blood. Regarding his diet, he preferred meat to vegetables and fruits. The patient had no family history of diabetes or urinary stones. He reported a 13% weight loss over one month. On admission, we observed moderate restlessness and Kussmaul breathing pattern. Blood test results showed a blood glucose level of 390 mg/dL, pH 7.106, base excess of –23.5 mmol/L, serum bicarbonate of 5.8 mmol/L, glycosylated hemoglobin (HbA1c) 11.3%, total ketone body level of 12853.0 µmol/L, and serum C-peptide level of 1.0 ng/mL (**Table 1**). His ionized calcium level was mildly elevated owing to intravascular dehydration (**Table 1**). Urinalysis revealed acidic urine

(pH < 5.0) and ketonuria (4+) (**Table 1**). The patient was diagnosed with moderate DKA based on the definition provided by the International Society of Pediatric and Adolescent Diabetes (1). Treatment was initiated with a 0.9% saline bolus and a continuous insulin infusion (0.05 units/kg/h). Hyperglycemia and ketoacidosis gradually improved after 14 h. The 24-h urinary C-peptide level was 2.9 µg/d (reference range [rr]: 22.8–155.2 µg/d). The anti-insulin autoantibody (1.1 U/mL [rr < 0.4 U/mL]) and insulinoma-associated antigen-2 autoantibody (28 U/mL [rr < 0.6 U/mL]) levels were increased. However, the anti-glutamic acid decarboxylase antibody level was not > 5.0 U/mL (rr < 5.0 U/mL). The patient was diagnosed as having autoantibody-positive T1D. The patient developed intermittent left lower abdominal pain three days after admission with no costovertebral angle or rebound tenderness. Twelve hours after the appearance of the abdominal pain, the pain exacerbated and radiated to the back. Urinary stones were suspected, and urinalysis revealed 20–29 red blood cells/high-power field and calcium oxalate crystals (**Table 1** and **Fig. 1A**). Computed tomography (CT) (cross-sectional images) revealed a high-density left ureteric mass (3 × 2 mm in size) (**Fig. 1B**), suggestive of a urinary stone. The fragmented left ureteric stone passed spontaneously a day after administering a 0.9% saline bolus. Follow-up CT revealed no urinary stones. The patient was discharged a week after admission without complications such as DKA or urinary stones (**Table 1**). He was readmitted to our hospital 3 months after discharge to investigate the etiology of the urinary stones. Spot urinalysis and a 24-h urine collection were performed. High urine sodium excretion was not observed. Urinary calcium, uric acid, citrate, cystine, and oxalate levels were within normal ranges (**Table 2**). This indicated the idiopathic etiology of the urinary stones in this patient with T1D. Hence, we recommended that he reduce the intake of meat, consume fruits/vegetables, and increase the intake of fluids to prevent recurrent urinary stone episodes. During his latest visit at 13 yr of age, the patient's blood glucose and HbA1c levels were well-controlled with subcutaneous insulin injections using a basal-bolus regimen. Urinalysis did not reveal low pH, hematuria, or oxalate crystals.

This study complied with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Kurume University (approval number: 2021-059). Written informed consent was obtained from the patient's parents for the publication of this case report and accompanying images.

Discussion

We have reported the case of a 12-yr-old Japanese adolescent boy diagnosed with new-onset T1D, DKA, and concomitant urinary stones.

Calcium oxalate stones are the most common type of urinary stone, followed by calcium phosphate stones, in children and adults. Both types of stones account for

Table 1. Patient's blood and urine laboratory values at first admission

Parameter		Day 0	Day 3	Day 7	Reference range
Blood					
pH		7.106	7.378	7.353	7.35–7.45
PCO_2	mmHg	19.3	32.4	48.3	35.0–48.0
HCO_3^-	mmol/L	5.8	18.7	26.2	22.0–29.0
BE	mmol/L	−23.5	−5.4	0.2	−3.0–3.0
RBC	×10⁶/μL	5.91	5.08	4.46	4.5–5.3
Hb	g/dL	15.4	13.5	12	13.0–16.0
Hct	%	47.5	38.2	37	37.0–49.0
WBC	×10³/μL	6.5	6.3	4.1	4.5–13.5
Plt	×10³/μL	375	220	314	150–400
AST	U/L	12	20	30	5–45
ALT	U/L	15	10	28	5–45
LDH	U/L	147	205	189	120–330
TP	g/dL	6.9	6.1	5.7	6.4–8.1
Alb	g/dL	4.6	3.9	NA	4.0–5.3
BUN	mg/dL	12	10	10	7–18
Cr	mg/dL	0.53	0.8	0.53	0.5–1.0
UA	mg/dL	6.6	3.1	NA	3.0–7.7
Na	mmol/L	133	133	138	136–146
K	mmol/L	3.9	2.7	4.8	3.5–5.0
Cl	mmol/L	101	98	103	98–106
Ca	mg/dL	9.3	8.9	8.9	8.4–10.2
Ca^{2+}	mmol/L	1.39	1.24	NA	1.12–1.23
P	mg/dL	3.5	4.3	4.5	2.9–5.4
Mg	mg/dL	1.92	NA	NA	1.5–2.3
p-Osm	mOsm/kg	303	NA	NA	275–295
Amy	U/L	84	45	NA	30–100
T-Chol	mg/dL	224	NA	NA	124–217
CK	U/L	61	48	NA	5–130
Glucose	mg/dL	390	340	NA	70–105
HbA1c	%	11.3	NA	NA	3.0–6.2
Serum total ketone	μmol/L	12853	5315	121	100–500
Lactate	mmol/L	1.6	1	NA	0.6–0.9
TSH	mIU/L	0.663	NA	0.728	0.61–4.23
$F.T_4$	ng/dL	0.62	NA	1.31	0.93–1.70
Anti-insulin Ab	U/mL	1.1	NA	NA	< 0.4
Anti-GAD Ab	U/mL	< 5.0	NA	NA	< 5.0
IA-2 Ab	U/mL	28	NA	NA	< 0.6
IRI	μU/mL	7.4	NA	NA	4–38
CPR	ng/mL	1	NA	NA	0.8–2.5
Urine					
Specific gravity		1.031	1.03	1.037	1.002–1.030
pH		< 5.0	6.5	6	4.5–8.0
Protein	mg/dL	30	±	−	−
Glucose	mg/dL	> 1000	> 1000	> 1000	−
Ketone		4+	3+	−	−
Occult blood		1+	2+	−	−
Red blood cell	high-power field	NA	20–29	< 1	0–2
White blood cell	high-power field	NA	< 1	1–4	0–3
Ca/Cr ratio		NA	NA	0.13	< 0.21
UA/Cr ratio		NA	0.43	NA	< 0.5
FENa	%	NA	NA	0.39	0.5–1.0
Calcium oxalate crystal		NA	+	−	−

Day 0, Admission day; Day 7, Discharge day; BE, base excess; RBC, red blood cell; Hb, hemoglobin; Hct, hematocrit; WBC, white blood cell; Plt, platelet; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; TP, total protein; Alb, albumin; BUN, blood urea nitrogen; Cr, creatinine; UA, uric acid; Na, natrium; K, kalium; Cl, chloride; Ca, calcium; P, phosphate; Mg, magnesium; p-Osm, plasma osmolality; Amy, amylase; T-chol, total cholesterol; CK, creatine kinase; HbA1c, hemoglobin A1c; TSH, thyrotropin; F.T₄; free thyroxine; Ab, antibody; GAD, glutamic acid decarboxylase; IA-2, insulinoma-associated antigen-2; IRI, immunoreactive insulin; CPR, C-peptide immunoreactivity; FENa, fractional excretion of sodium; NA: not available.

A

B
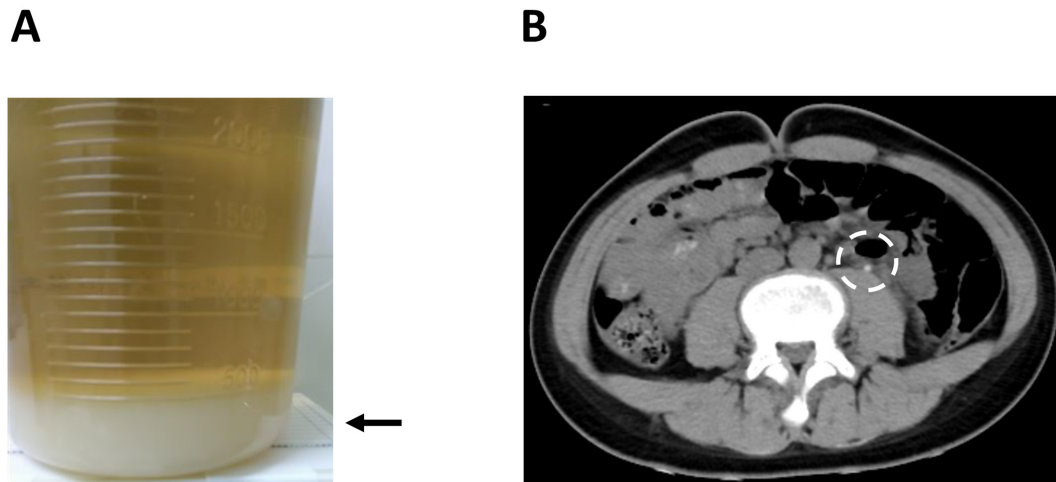
Fig. 1. Patient's clinical findings. (A) Photograph of patient's urine. Urinary calcium oxalate crystals settled at the bottom of the bottle (indicated by the arrow). (B) Abdominal computed tomography image. The dashed circle indicates the stone located in the left ureter.

Table 2. Patient's urinalysis at the second admission

Parameter		Value	Normal range
Spot urine test			
Specific gravity		1.032	1.002–1.030
pH		5.5	4.5–8.0
Protein	mg/dL	±	–
Glucose	mg/dL	–	–
Ketone		±	–
Red blood cell	high-power field	< 1	0–2
White blood cell	high-power field	1–4	0–3
Ca/Cr ratio		0.036	< 0.21
UA/Cr ratio		0.3	< 0.5
FENa	%	0.2	0.5–1.0
Citrate	mg/L	832	138–1010
Cystine	nmol/mg.cr	8.5	23.2–125.9
Calcium oxalate crystal		–	–
24-hour urine storage test			
Oxalate	mg/d	27.9	10.3–41.5
Protein	mg/d	99	31–120

Ca, calcium; Cr, creatinine; UA, uric acid; FENa, fractional excretion of sodium.

80% of all urinary stones (4, 12). We could not confirm the composition of the urinary stone in this patient as it passed spontaneously. However, it would be reasonable to assume that it was a calcium oxalate stone based on the detection of calcium oxalate crystals in the urinalysis. Urinalysis was performed when the stone was detected on CT.

To date, only four patients, one adult and three children, have been reported to develop urinary stones upon DKA admission (11, 13). Of the three children with new-onset T1D, 24-h urine collection was performed in two, revealing that one child had high urine sodium levels and the other had low urine citrate excretion (11). In a study by Yuno *et al*. (the article is written in the Japanese language), one adult with T1D developed ammonium acid urate crystals (13). Notably, urinary

stones developed in those pediatric patients with DKA who had risk factors such as high urine sodium and low urine citrate excretion. This is consistent with the previous observations. Metabolic disorders such as hypercalciuria, hyperuricosuria, hypocitraturia, cystinuria, and hyperoxaluria have been reported in 12–50% of pediatric patients with urinary stones (12, 14). We initiated a comprehensive evaluation of the patient, including urinalysis and blood tests. Except for T1D, this evaluation revealed no evidence of metabolic disorder. Children with diabetes mellitus experience varying degrees of dehydration and electrolyte imbalance owing to osmotic diuresis (1, 2). Dehydration leads to low urine output, which increases the calcium and phosphate concentrations in the urine and the risk of stone formation (9, 10). Physical findings and laboratory data

showed that our patient was dehydrated on admission, and hyperglycemia-associated dehydration due to DKA resulted in stone formation. Moreover, patients with type 2 diabetes mellitus (T2D) have significantly higher quantities of urinary oxalate and lower urinary pH than those without diabetes mellitus. This combination may be attributed to changes in intestinal absorption, colonization by Oxalobacter formigenes, and increased endogenous oxalate production (6, 7). Maalouf *et al.* reported that the urinary pH was significantly lower in patients with T2D than in controls (8). Both local and systemic acidosis increase intestinal phosphate absorption and phosphate release from the bone. This increases blood phosphate levels and urinary phosphate excretion (10). Additionally, systemic acidosis downregulates the expression and activity of calcium channels in the distal and connecting tubules. Therefore, urinary calcium excretion increased (10). Although the urinary electrolyte data of our patient were unavailable, he had hyperglycemia, low urinary pH, and acidosis on admission. Based on the above laboratory values, it seems reasonable to conclude that dehydration, DKA-induced hyperglycemia, low urinary pH, and acidosis were associated with the urinary stone formation in our patient.

Subsequently, we focused on the possible association between a patient's unbalanced diet and the formation of calcium oxalate crystals. Our patient preferred meat and rarely consumed vegetables or fruit. Meschi *et al.* reported that the withdrawal of vegetables and fruits from the diet of healthy adults causes a decrease in the urinary excretion of citrate and oxalate (15). Similarly, excessive intake of animal protein leads to increased urinary calcium and oxalate excretion and decreased urinary citrate excretion (3, 9, 14, 16, 17). Citrates increase the solubility of stone-forming calcium salts and inhibit the growth and aggregation of calcium oxalate crystals (3, 4, 14, 18). On the basis of these reports,

we speculate that the patient had hypercalciuria, hypocitraturia, and/or hyperoxaluria. However, as his urinary calcium, citrate, and oxalate levels were within the normal range, it seems unlikely that the imbalanced diet could have contributed to calcium oxalate crystal formation.

Due to volume depletion in both the intra- and extracellular fluid compartments, acute kidney injury, which is associated with an increased risk of chronic kidney disease, is prevalent in children and adolescents admitted with DKA (19, 20). One or more urinary stone episodes are associated with an increased risk of end-stage renal disease (adjusted hazard ratio [HR], 2.16) and chronic kidney disease (HR, 1.74) (14). Therefore, recognizing the risk of urinary stone development in patients with DKA is essential for preventing subsequent kidney damage.

Conclusion

Here, we have documented the case of a 12-yr-old adolescent boy with urinary stones and concomitant DKA. DKA-induced dehydration, hyperglycemia, low urinary pH, and acidosis may be associated with the formation of calcium oxalate crystals. Therefore, physicians should consider urinary stone formation in DKA patients.

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