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CASE REPORT

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Uric acid stones following hepatic transplantation

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Abstract We report the case of a 52 year old man with a history of insulin-requiring diabetes and hepatitis B with cirrhosis who received an orthotopic liver transplant. One year later he developed renal colic and was found to have a 3 mm stone at the left ureterovesical junction. Numerous other stones formed and infrared spectroscopy analysis demonstrated all to be composed of 100% uric acid. Urine collections demonstrated a low urine pH of 5.1 without hyperuricosuria. His stones were effectively prevented with potassium citrate therapy. Few incidence data are available for uric acid stone occurrence in solid organ recipients. Calcineurin inhibitors are thought to often cause hyperuricemia on the basis of decreased urate excretion. However, this effect would not be expected to cause hyperuricosuria nor uric acid stones. This class of drugs may also be associated with low urine pH, perhaps on the basis of hypoaldosteronism, but the contribution of such a syndrome to uric acid stone formation is not established.

Keywords FK-506 · Hyperuricosuria · Tacrolimus/urine/adverse effects · Kidney calculi/chemistry/etiology · Urolithiasis

Introduction

The calcineurin inhibitors cyclosporine and tacrolimus are the basis of modern immunosuppressive regimens used to prevent the rejection of organ transplants. An association of calcineurin inhibitors with uric acid nephrolithiasis has been reported, but the mechanism is not described [1, 2]. We report a case of uric acid nephrolithiasis following liver transplantation, and review the possible pathophysiology.

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Case report

The patient is a 52-year-old man with hypertension, adult-onset, insulin-requiring diabetes mellitus, and chronic hepatitis B with cirrhosis and variceal bleeding. There was no previous history of urolithiasis. He received an orthotopic liver transplant, and was treated with tacrolimus, prednisone, lansoprazole, and trimethoprim/sulfamethoxazole, and continued the medications he took prior to the transplant: lamivudine, insulin, amlodipine, and atenolol. Prednisone was discontinued by the time he presented with his first episode of kidney stones, 12 months after the transplantation. At that time he was admitted to the hospital with renal colic and a 3 mm stone at the left ureterovesical junction with mild hydronephrosis. His height was 166 cm, his weight 83 kg and his calculated body mass index was 30 kg/m^2; he had gained 5 kg since his hepatic transplantation. Two small stones were also present on CT scanning near the ureteropelvic junction. Urinalysis showed 4+ glycosuria, no hematuria, pyuria or proteinuria, pH 5.5. A urine culture was negative. Complete blood count was normal with WBC 4.3/ml. The serum creatinine concentration was 1.7 mg/dl. The tacrolimus level was 11.4 ng/ml. A cystoscopy was negative and the stone passed. At discharge, the patient's creatinine concentration was 1.4 mg/dl. At that time his estimated GFR, using the MDRD equation [3], was 57 ml/min/1.73 m^2.

In the subsequent months he formed innumerable small stones, some of which caused renal colic. All of the stones were passed spontaneously. Stone analysis by infrared spectroscopy revealed 100% uric acid.

Serum chemistry results are shown in Table 1. The serum uric acid concentration was not obtained at the

Table 1 Serum values pre- and post-translation. NA not available. Uric acid was obtained several months after admission for stones, at the time of an initial admission for renal colic

Serum values	Pre-transplant	One year post-transplant
Sodium (mM/l)	128	142
Potassium (mM/l)	4.0	4.6
Chloride (mM/l)	93	103
Bicarbonate (mM/l)	24	25
BUN (mg/dl)	55	26
Creatinine (mg/dl)	1.4	1.7
Glucose (mg/dl)	223	383
Calcium (mg/dl)	7.6	8.5
Magnesium (mg/dl)	2.4	1.5
Phosphate (mg/dl)	5.0	2.0
Uric acid (mg/dl)	NA	5.1
Hemoglobin A1c (%)	NA	8.0
AST (U/l)	57	38
ALT (U/l)	66	37
Alkaline phosphatase (U/l)	103	80
T. Bili (mg/dl)	4.2	0.7
D. Bili (mg/dl)	0.8	<0.1
Total protein (g/dl)	6.3	7.1
Albumin (g/dl)	3.3	4.2

time of the first stone passage but several months later in the kidney stone clinic. Urinalyses pre-transplant showed glycosuria with urine pH values of 6.0, 5.0 and 6.0. At presentation with stones, a year after the transplant, a urinalysis showed pH 5.5, specific gravity 1.024, glycosuria, and no proteinuria.

Three 24-h urine collections were performed before the initiation of treatment for uric acid stones. These were analyzed by Litholink (Chicago, Ill., USA). As the results of the urine collections were similar, the mean values are listed in Table 2. The significantly elevated supersaturation of uric acid was consistent with uric acid stone formation. The patient did not have significant hyperuricosuria; the major contributor to his elevated uric acid supersaturation was instead attributable to the very low 24-h urine pH. The patient was treated with potassium citrate 30 mEq twice a day, with a subsequent urine pH of 7.5. There was no recurrence of uric acid stone formation.

Table 2 Results of 24 h urine collections. CaOx calcium oxalate, CaP calcium phosphate, normal values (in parentheses) provided by Litholink (Chicago Ill.)

24 h urine	Mean results of three samples
Volume (l/d) (0.5–4)	1.92
Creatinine (mg/d)	1,515
Urine pH (5.8–6.2)	5.06
Supersatuation uric acid (0–1)	2.7
Uric acid (g/d) (men <0.8)	0.71
NH_4 (mM/d) (15–60)	48
Sulfate (mEq/d) (20–80)	47
Urea nitrogen (g/d) (6–14)	13.9
Citrate (men >450)	661
Supersatuation CaOx (6–10)	3.1
Supersatuation CaP (0.5–2)	0.1
Calcium (md/d) (men <250)	143
Oxalate (mg/d) (20–40)	34
Phosphate (g/d) (0.6–1.2)	0.92
Sodium (mM/d) (50–150)	260
Potassium (mM/d) (20–100)	55
Chloride (mM/d) (70–250)	258
Magnesuim (mg/d) (30–120)	126

Discussion

This is the first report, to our knowledge, of post-hepatic transplant uric acid stones. Although cyclosporine has been said to "often" cause the formation of uric acid stones [4], there are relatively few detailed data reporting the incidence or prevalence of uric acid stones associated with solid organ transplantation or the use of these drugs in other settings. Case reports of uric acid stones following kidney transplants have been described since 1976. One report found that 16 of 794 (2%) of renal transplant recipients transplanted between 1981 and 1996 had upper urinary tract stones, at least half of which were composed of uric acid [5]. In another study of pediatric kidney recipients, transplanted between 1973 and 1988, 652 patients had 33 stones, six of which were composed of uric acid, a prevalence of about 1% [6]. Another report from 1988 noted nine stones, only one of which was composed of uric acid, among 544 kidney transplant recipients [7]. Overall reported rates of uric acid stones range from 0.2% to 3.0% among kidney transplant recipients.

Uric acid stone formation requires supersaturation of urinary uric acid. Three factors contribute to this variable: low urine pH, hyperuricosuria, and low urinary volume [8, 9, 10].

Uric acid has a physiologically significant dissociation constant of about 5.35 at 37°C. Its solubility product constant (k_{sp}) is about 96 mg/l [8]. At pH values of 4.5, 5.5, and 6.5, total uric acid concentrations of about 110, 200, and 1,100 mg/l, respectively, are required to exceed solubility [10]. For a given patient with a stable dietary intake of purines, therefore, urine pH is the most important factor for uric acid stone formation.

Definitions of hyperuricosuria vary from 600 to 800 mg per day. Hyperuricosuria may be associated with hyperuricemia. Calcineurin inhibitors such as cyclosporine and tacrolimus are known to cause hyperuricemia relatively frequently [11]. The proposed mechanism is increased proximal tubular urate reabsorption, or decreased urate secretion [12]. In the absence of concomitant increased synthesis of uric acid, increasing urate reabsorption may account for hyperuricemia, but it would not be expected to account for hyperuricosuria.

The calcineurin-inhibitor era began in the late 1980s. In 1988, Dieckmann et al. reported a case of pure uric acid stones in a 21-year-old renal transplant patient after 3 years of cyclosporine maintenance therapy. Other findings were a urine pH of 5.0 and persistent hyperuricemia [1]. The authors identified only four previous cases of uric acid stones following renal transplantation

in the literature. In 1991, Cantarell et al. also reported new uric acid nephrolithiasis in kidney transplant patients maintained on cyclosporine [2]. The authors suggested that the use of cyclosporine had led to an increase in uric acid stone incidence post-renal transplant and offered some unique data. Stones occurred among 3% of 365 transplant recipients and at equal rates in the groups of patients prescribed azathioprine or cyclosporine. Among the patients receiving azathioprine, however, all stones were composed of calcium salts. Among patients receiving cyclosporine, on the other hand, 60% of stones were composed of uric acid. Compared with patients maintained on azathioprine, the cyclosporine group had a lower average urine pH (5.1 ± 0.3 vs. 5.7 ± 0.7), higher serum uric acid level (8.3 ± 1.4 vs. 6.2 ± 1.9 mg/dl), lower urate clearance and urate fractional excretion. We are aware of no other data demonstrating that calcineurin inhibitors have been associated with an increase in uric acid stone formation in solid organ transplant recipients.

Urine pH varies during the day based on the fluid intake and diet. It likely needs to be less than 5.5 for at least 12 of 24 h to be significantly low enough to contribute to uric acid stone formation [13]. The pathophysiology of persistent urinary acidity remains unclear in patients with a tendency to form uric acid stones. Decreased ammonia excretion is one suggested mechanism [14, 15]. However, studies of ammonia excretion in uric acid stone formers yield inconsistent results [10]. Proposed factors or mediators that affect ammoniagenesis include age, prostaglandins, insulin, parathyroid hormone, angiotensin II, growth hormone, and glucocorticoids [16, 17]. Administration of the latter to dogs is associated with an increase in net acid excretion and a decrease in urinary pH [18]. Dietary protein intake also contributes to net daily acid excretion, resulting in a lower urinary pH [19]. Our patient, as judged by his urinary sulfate excretion, was on a moderate proton-generating diet, and this may have played a further role in his having a low urine pH. We do not believe that his dietary proton intake changed after, as compared with before, his hepatic transplantation.

In our patient, hyperuricosuria was not present. Instead, his uric acid stones were evidently caused by low urine pH. Older age, diabetes with insulin resistance, and steroid use may be factors contributing to the intermittent low urine pHs of our patient before the transplant. Recent data have highlighted the possible links between increased body weight and insulin resistance, resulting in low urinary pH and uric acid stones [20, 21, 22]. It is possible that his low urine pH was in part related to his insulin resistance. However our patient had diabetes both before and after his liver transplant with no obvious differences in the level of diabetic control. However, he had gained 5 kg since the transplant and at 30 kg/m^2 now met the criterion for obesity, which may have contributed to his low urine pH.

One study suggests that tacrolimus is associated with distal renal tubular acidosis (RTA) in that generation of CO_2 in an alkaline urine, a measure of proton secretion, was impaired by tacrolimus [23]. Distal RTA should be associated with a higher urine pH and a negligible risk of uric acid stones. However the patients in this study at baseline had relatively low urine pH values, but no uric acid stones were cited in this report.

Do calcineurin inhibitors directly interfere with ammoniagenesis? We are not aware of any data to support this effect. However, calcineurin inhibitors are also known to cause type IV RTA with hyperkalemia and hyporeninemic hypoaldosteronism [23, 24]. This form of RTA is most often attributed to the inhibition of ammoniagenesis by hyperkalemia, in turn attributed to hypoaldosteronism. This condition is accompanied by low urine pH, as acidification of the urine is not impaired, and acidosis, as proton excretion is limited by the lack of lumenal buffer that results from impaired ammoniagenesis. However, renal calculi are uncommon in patients with type IV RTA who have not received organ transplants [25]. Uribarri et al. suggest that the major protection from renal calculi in such patients is impaired glomerular filtration and the ensuing reduction in the excretion of stone-forming substances such as uric acid [26]. However, if hyperuricosuria is present in the context of type IV RTA, uric acid calculus formation could occur. Type IV RTA is quite unlikely in our patient, who did not have hyperkalemia. If calcineurin inhibitors impaired ammoniagenesis, then a low urine pH would result without hyperkalemia.

It was not possible to implicate other drugs the patient was taking in contributing to the low urine pH. Trimethoprim, used in combination with sulfamethoxazole, for prophylaxis of post-transplant pneumocystiis pneumonia, can cause renal tubular acidosis. However, this drug, by blocking amiloride-inhibitable epithelial sodium channels (ENaC) in the cortical collecting duct, impairs proton secretion [27]. This effect accounts for the association of trimethoprim with distal, or Type I, voltage-dependent renal tubular acidosis, and an inappropriately high, not low, urine pH.

It is striking that few data, if any, have investigated the lithogenicity of urine both before and after solid organ transplantation, and many reports of post-transplant stones are lax in relating stone composition and prevalence to specific medication regimens. We believe that this patient represents the first report of uric acid stones following hepatic transplantation, that his stones were attributable to low urine pH, and that this effect was multifactorial, with an important contribution of the calcineurin inhibitor tacrolimus.

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