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An Unusual Case of Acute Phosphate Nephropathy

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INTRODUCTION

Acute phosphate nephropathy (APN) is a form of kidney injury that classically occurs following the use of bowel purgatives and enemas that contains oral sodium phosphate (OSP). We present here an unusual case occurring in the setting of OSP replacement use in a patient without pre-existing renal impairment.

CASE PRESENTATION

A 27-year-old Chilean woman was referred to the emergency department by her general practitioner with an acute kidney injury and electrolyte disturbance. She reported symptoms consistent with tetany on a background of persistent nausea and vomiting. She had been admitted to the internal medicine unit 2 months earlier with hypokalemia and hypophosphatemia (Table 1) associated with longstanding vomiting episodes that had been investigated extensively, including with endoscopy 6 months prior to presentation, without an identifiable underlying cause. A diagnosis of bulimia nervosa had been considered. She was discharged from hospital at this time with oral effervescent potassium tablets and oral effervescent sodium phosphate tablets (Table 2). She was advised to take the phosphate tablets while she still experienced the vomiting episodes to prevent the re-development of hypophosphatemia.

The patient re-presented to hospital with nausea, vomiting, and muscle cramps. Initially on presentation, her ionized calcium was 0.85 mmol/l and serum phosphate was elevated at 3.22 mmol/l (Table 1). She had developed an acute kidney injury with serum creatinine of 265 μmol/l (Table 1). Urine electrolytes showed low calcium excretion; unfortunately urine phosphate excretion was not available (Table 3). Oral phosphate tablets were ceased, and she was given slow i.v. calcium, magnesium, and i.v. normal saline solution at a rate of 125 ml/h with rapid improvement in serum electrolytes over the next 48 hours; however her serum creatinine remained elevated at 220 μmol/l.

There were no new medications or the development of new symptoms, and the patient denied being unable to tolerate oral fluids between the vomiting episodes. Upon detailed history taking, it became apparent that the patient had been taking phosphate tablets after every vomiting episode, as she believed that these would replace nutrients that she had lost with the emesis. Unfortunately, this meant that she had been taking in excess of 10 tablets on most days. Urinalysis showed bland sediment with no detectable proteinuria and a pH of 7.5 with specific gravity of 1.020. Ultrasound findings of the kidneys and urinary tract were unremarkable. She was not hypotensive at any point, and there were no features to suggest an extrarenal inflammatory disorder.

Given the markedly elevated serum phosphate and the metabolic alkalosis with a serum pH of 7.60, pCO_2 of 41 mm Hg, and bicarbonate 37 mmol/l, the possibility of acute phosphate nephropathy was considered, and a renal biopsy was undertaken. Histology demonstrated scattered foci of calcification with tubule lumens (Figure 1) and in some areas within tubular epithelial cells that stained positive with the von Kossa stain (Figure 2).

DISCUSSION

APN and nephrocalcinosis occur in association with a range of disease processes that lead to elevations of calcium or phosphate in the blood or urine, including sarcoidosis, malignancy, medullary sponge kidney,

Table 1. Relevant laboratory parameters

Serum laboratory parameters	At initial presentation	Recovery from initial presentation	Second presentation	Follow-up 7 months after discharge
Sodium (135–145 mmol/l)	133	138	144	136
Potassium (3.5–5.2 mmol/l)	2.6	2.8	4.1	2.3
Chloride (95–110 mmol/l)	85	99	81	95
Bicarbonate (22–32 mmol/l)	37	26	36	32
Magnesium (0.70–1.10 mmol/l)	0.64	1.19	0.79	0.85
Corrected calcium (2.10–2.60 mmol/l)	2.35	2.40	2.20	2.44
Ionized calcium (1.13–1.32 mmol/l)	1.08	N/A	0.85	N/A
Phosphate (0.75–1.50 mmol/l)	1.29	1.00	3.22	0.95
Creatinine (45–90 μmol/l)	71	72	265	89
eGFR (>90 ml/min per 1.73 m^2)	>90	>90	21	76
Urea (2.5–7.5 mmol/l)	4.6	2.3	7.1	5.6

eGFR, estimated glomerular filtration rate.

and rare inherited diseases such as Dent disease and cystinosis. There has been significant literature regarding the role of OSP bowel preparations. OSP preparations act as purgatives by causing excretion of water into the intestinal lumen to maintain isotonicity, which leads to colonic evacuation. This can lead to 1 to 1.8 L of hypotonic fluid loss after a single 45-ml dose of OSP.[1] In 1 example, a patient developed extreme hypernatremia that resulted in central pontine myelinolysis.[2]

Acute phosphate nephropathy is proposed as a result of multiple mechanisms including increased proximal salt and water reabsorption as a result of hypovolemia, a large phosphate load arriving in the distal nephron, and the consequent precipitation of calcium phosphate in the distal nephron.[3] Most renal phosphate reabsorption occurs in the proximal tubules, with only small amounts reabsorbed by the distal nephron. A study in 5 patients receiving OSP found a marked reduction in urinary calcium excretion that is consistent with calcium phosphate precipitation.[4]

Diagnostic criteria used for the identification of APN included the following: acute kidney injury, recent exposure to OSP, renal biopsy findings of diffuse tubular injury with abundant calcium phosphate deposits, no evidence of hypercalcemia, and no other significant pattern of renal injury.[5]

Table 2. Medications at presentation

Sodium phosphate tablets (500 mg elemental phosphorus per tablet): 2 tablets three times daily after vomiting
Potassium chloride tablets (14 mmol potassium per tablet): 2 tablets three times daily
Magnesium aspartate 500-mg tablets: 1 tablet daily

Table 3. Urine electrolyte studies

Urine electrolyte parameters	
Volume (L)	2.02
Creatinine excretion per 24 hours (9.0–18.0 mmol/24 h)	6.5
Sodium excretion (130–250 mmol/24 h)	149
Potassium excretion (25–90 mmol/24 h)	67
Calcium excretion (2.50–7.50 mmol/24 h)	<1.0
Phosphate excretion (mmol/24 h)	N/A
Protein excretion (g/24 h)	<0.14

Some patients present acutely with elevated serum phosphate; however, kidney injury may become apparent weeks or months following exposure to the sodium phosphate preparations.[6] Risk factors for acute phosphate nephropathy include older age, female sex, hypertension, chronic kidney disease, and treatment with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and diuretics.[3] Of these risk factors, our patient's only risk factor was her sex. The exact mechanism by which hyperphosphatemia causes kidney injury is not known; however, there are a few hypotheses. Transient hyperphosphatemia leads to an increased intratubular phosphate concentration, resulting in the precipitation and tissue deposition of calcium phosphate salts that cause luminal obstruction, direct tubular epithelial injury, and activation of the immune response.[1,3] A cohort of patients with APN found that 19% of patients with APN progressed to end-stage kidney disease; of the remaining patients, none returned to baseline kidney function, and only 19% reached a serum creatinine of <176 μmol/l.[5]

The classic cause of APN is the use of OSP as a purgative; however, our search of the literature

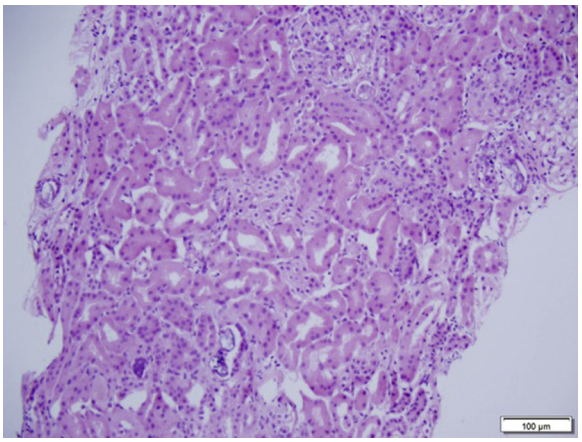

Figure 1. Renal biopsy specimen with light microscopy and hematoxylin and eosin staining. Arrows show scattered foci of calcification in the tubular lumen without evidence of other renal pathology.

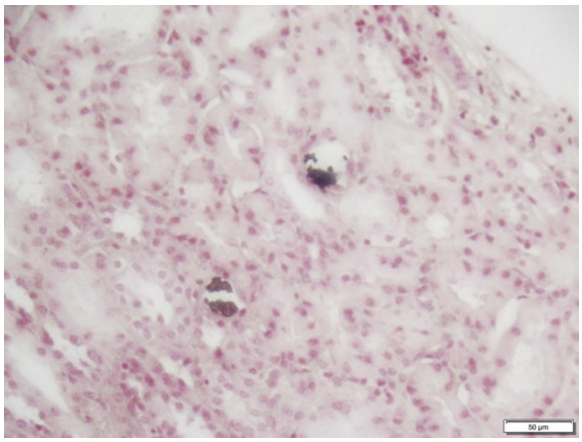

Figure 2. Renal biopsy specimen with light microscopy and von Kossa staining. Asterisks show calcium phosphate crystals in the tubular lumen staining with the von Kossa stain.

identified cases of APN that occurred outside this setting, and these are summarized in Table 4. Several of these cases occurred with either a large phosphate load either with[7–9] or without[S1] an insult, leading to either dehydration or kidney underperfusion.

A case was reported of a 36-year-old man with delayed kidney allograft function following transplantation who was severely hyperphosphatemic before transplantation and remained so until the initiation of posttransplantation hemodialysis.[S2] This patient did not receive any phosphate-containing medications, either before or after the kidney transplantation. Another case of posttransplantation APN was reported in 2 recipients of deceased-donor kidneys from a donor who had received i.v. phosphate for treatment of hypophosphatemia associated with diabetic ketoacidosis.[8] This caused APN, which was initially unrecognized and resulted in poor kidney allograft outcomes in the 2 recipients.

Many of these cases had multiple factors that likely contributed to kidney calcium phosphate precipitation. In 1 case in which oral phosphate supplementation was identified, volume depletion from diarrhea, prior tubular injury, hyperparathyroidism, and high serum tacrolimus concentration leading to a high urinary phosphate load to a single kidney were observed.[9]

One recorded case occurred in conjunction with a high phosphate load and the use of urinary alkalization for the treatment of tumor lysis syndrome.[S3] Calcium phosphate precipitation is favored by an alkaline environment,[S4] and we suspect that APN risk is increased in circumstances in which the urine is deliberately alkalinized as in the above case, or in which the loss of hydrogen ions from chronic vomiting leads to systemic alkalosis and the passage of

Table 5. Teaching points

Acute phosphate nephropathy can result from oral phosphate supplementation in a patient without known renal impairment
The mechanism in our patient was multifactorial, including large ingested phosphate load, likely a degree of volume contraction relating to vomiting, and secondary reduced renal tubular ultrafiltrate flow. Chronic vomiting led to alkalosis, which promotes the crystallization of calcium phosphate, as seen in this case.

Table 4. Examples of cases of APN without exposure to OSP bowel preparation

Case	Source of phosphate	Reference
47-Yr-old man with high anion gap metabolic acidosis secondary to ethylene glycol intoxication treated with i.v. sodium phosphate. Resulted in temporary dialysis-dependent kidney failure	i.v. sodium phosphate	Parmar *et al.*[S1]
28-Yr-old man following a car accident who developed phosphate nephropathy in the setting of rhabdomyolysis	Release of intracellular phosphate stores	Monfared *et al.*[7]
Patient with tumor lysis syndrome treated with rasburicase and urine alkalinization	Release of intracellular phosphate stores	El-Husseini *et al.*[S3]
APN due to deliberate inhalation of monoammonium phosphate, a dry chemical powder present in fire extinguishers. Resulted in hyperphosphatemia, hypocalcemia, hypomagnesemia, seizures, and dialysis-requiring AKI	Monoammonium phosphate inhalation	Senthikumaran *et al.*[S5]
36-Yr-old male kidney transplant recipient with delayed graft function. He was severely hyperphosphatemic before transplantation.	Reduced phosphate clearance due to CKD and delayed graft function	Manfro *et al.*[S2]
Evolving APN in 2 deceased-donor renal transplants in which the donor had been given i.v. phosphate for treatment of hypophosphatemia associated with diabetic ketoacidosis. This was unrecognized initially and resulted in poor graft outcomes.	i.v. sodium phosphate	Agrawal *et al.*[8]
70-Yr-old renal transplant recipient who received oral potassium phosphate for undetectable serum phosphate 4 weeks after transplantation. Two weeks later she had an acute kidney injury with hypocalcemia and hyperphosphatemia. A kidney biopsy confirmed APN	The authors identified multiple contributing factors for calcium phosphate deposition: Oral phosphate supplementation Volume depletion Prior tubular injury Inappropriately elevated parathyroid hormone High tacrolimus levels Single kidney	Riella *et al.*[9]

AKI, acute kidney injury; APN, acute phosphate nephropathy; CKD, chronic kidney disease; OSP, oral sodium phosphate.

alkaline urine. This would compound the drive to calcium phosphate precipitation in circumstances in which a high calcium phosphate product was delivered to the renal tubules.

CONCLUSION

This appears to be the first case occurring in the setting of OSP replacement use in a patient without known renal impairment. We propose that the underlying mechanism of development was multifactorial, including the large ingested phosphate load, likely a degree of volume contraction relating to vomiting and secondary reduced renal tubular ultrafiltrate flow, and the alkalosis arising from chronic vomiting (Table 5). Alkalosis promotes the crystallization of calcium phosphate and is probably a significant factor driving the development of this condition in a young woman. As with other examples in the literature, our patient did not return to baseline renal function, but experienced a significant improvement in renal function that likely reflects her young age and relatively preserved renal reserve.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary References.

Supplementary material is linked to the online version of the paper at www.kireports.org.

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