

Acute Phosphate Nephropathy

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We present acute phosphate nephropathy in a 28-year-old man, which was developed after a car accident due to rhabdomyolysis. Treatment of acute kidney injury was done with administration of sodium bicarbonate.

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INTRODUCTION

Acute phosphate nephropathy is a form of kidney injury that occurs following the use of bowel purgatives which contains oral sodium phosphate and following the administration of sodium phosphate-containing enemas.^{1,2} Acute kidney injury (AKI) associated with an increased phosphate load has also been described in tumor lysis syndrome, especially with alkalization of the urine by bicarbonate-containing intravenous fluids. To our knowledge and based on a review of the literature acute phosphate nephropathy in the setting of rhabdomyolysis has not been reported. Thus, we report a patient with AKI due to acute phosphate nephropathy after a crush injury.

CASE REPORT

A 28-year-old man was referred to our hospital with AKI following a car accident and fracture of the right hip and pelvic and orthopedic surgery 7 days before admission. He had not had any medical or drug history before the accident. Blood pressure was 110/80 mm Hg before being transferred to our center. His serum creatinine and blood urea nitrogen levels were 1 mg/dL and 19 mg/dL before the surgery, respectively. Hemoglobin level was 14 g/dL; serum sodium, 142 mEq/L; serum potassium, 5.4 mEq/L; serum calcium, 8 mg/dL; serum phosphorus, 6 mg/dL; uric acid, 7 mg/dL; creatine phosphokinase, 12 000 µg/L; and lactate dehydrogenase, 18 000 IU/L. Also, he had been

treated with an aminoglycoside, a first generation of cephalosporins, and celecoxib. His urine output decreased gradually and serum creatinine rose to 7 mg/dL, and then he was referred to our center. His blood pressure was 160 /97 mmHg; body temperature was 38°C. He was tachypenic, but the lungs and heart sounds were otherwise normal. Purulent secretion in the surgery region was seen. His serum creatinine level was 11 mg/dL; blood urea nitrogen, 120 mg/dL; hemoglobin, 8 g/dL; serum potassium, 6 mEq/L; serum sodium, 138 mEq/L; serum calcium, 7.4 mg/dL; serum phosphorus, 14.5 mg/dL; uric acid, 12 mg/dL; pH 7.14; partial pressure of carbon dioxide, 20; bicarbonate, 9 mEq/L; creatine phosphokinase, 12 500 µg/L; and lactate dehydrogenase, 14 300 IU/L. His urine microscopy showed many isomorphic erythrocytes and leukocytes per high-power field, 2 granular casts, and 1 leukocyte clump. Urinalysis revealed protein (2+), blood (2+), and pH 4.5. Urine culture was positive for *Escherichia coli*. The 24-hour urine protein, creatinine, and calcium were 950 mg, 1100 mg, and 195 mg, respectively. Normal kidney sizes and normal parenchymal echo without scarring were shown on ultrasonography. Calcification or calculus was not seen on plain radiography.

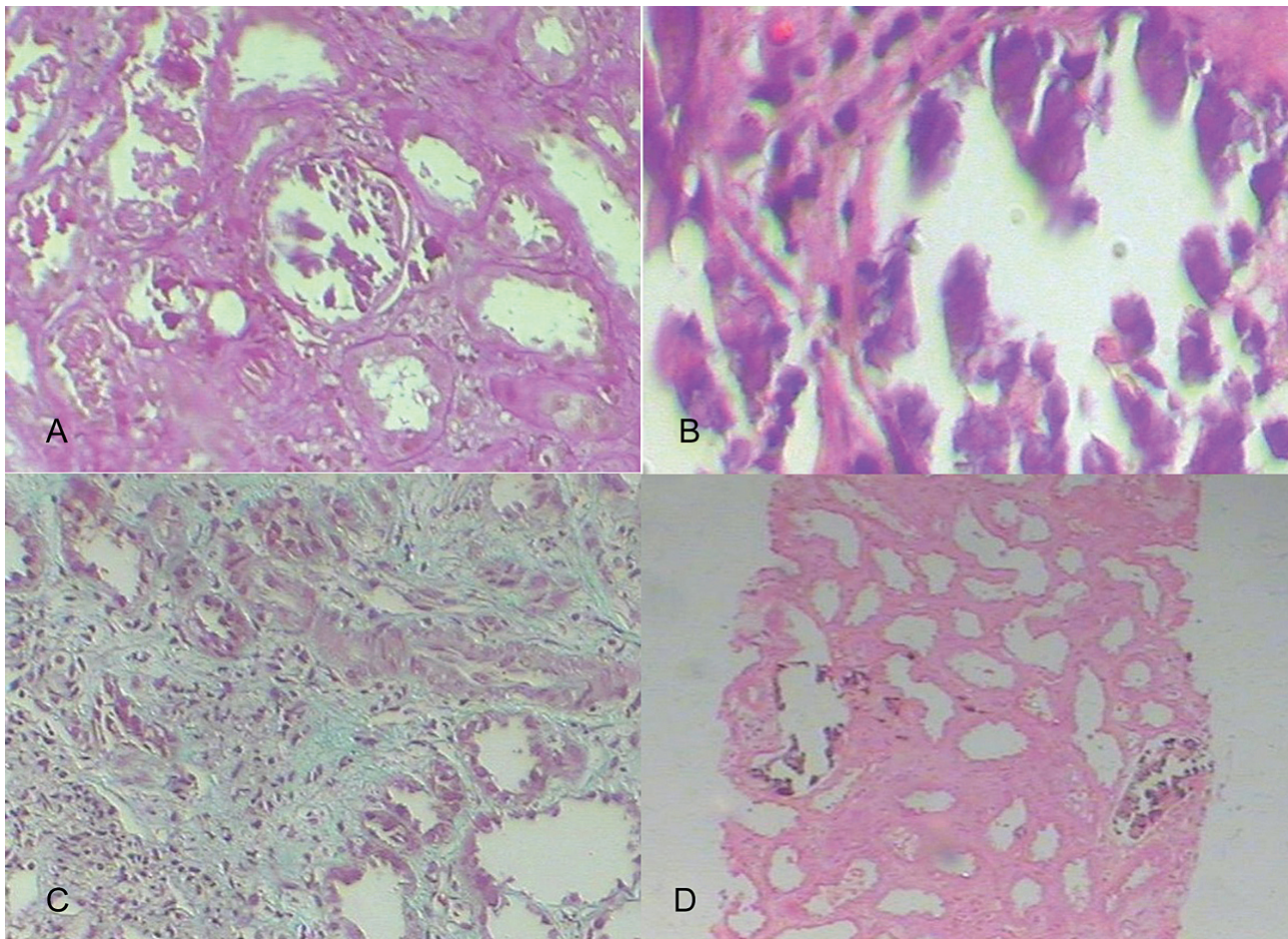
Optimum hydration with isotonic saline, alkalization with intravenous sodium bicarbonate solution and change of antibiotics, discontinuation of celexib, debridement of necrotic tissue, and hemodialysis were initiated, but after 15 days,

no recovery in kidney function was seen. Urine culture became negative. Ultrasonography-guided renal biopsy was performed and light microscopy revealed 7 glomeruli that were fairly normal; basement membranes were thin and regular without any glomerular hypercellularity, necrosis, or crescent formation. The interstitium showed significant fibrosis and chronic inflammation. Some tubules contained cellular debris and revealed epithelial injury and atrophic changes. Also, extensive foci of microcalcification were seen within the interstitium and tubules. These calcified areas were positive in von Kossa staining and revealed no birefringence under polarized light. The vessels were unremarkable (Figure).

The patient was discharged with hemodialysis, 2 sessions per week, but after 1 month, his serum creatinine decreased to 2 mg/dL; thus, hemodialysis was discontinued and chronic kidney disease management continued.

DISCUSSION

Differential diagnosis of AKI in our patient included ischemic acute tubular necrosis due to bleeding, toxic acute tubular necrosis due to aminoglycoside or rhabdomyolysis, or a combination of these. Also tubulointerstitial nephritis could be due to nonsteroidal anti-inflammatory drugs or cephalosporins. Urinalysis showed proteinuria, isomorphic hematuria, pyuria, granular cast, and leukocyte clamp. Normal blood pressure and no history of massive bleeding and urine microscopy are less likely to associate with ischemic acute tubular necrosis. Rhabdomyolysis is a good diagnosis candidate with regards to the history of crush injury and high levels of creatine phosphokinase, lactate dehydrogenase, potassium, phosphorus, and uric acid, together with hypocalcemia. Although in urine microscopy, we did not see pigmented casts, urinary findings can be seen in rhabdomyolysis. Aminoglycoside



A, Interstitial inflammation with tubular atrophy and calcium deposit (hematoxylin-eosin). **B**, Extensive interstitial and tubular calcification. **C**, Trichrom staining shows interstitial fibrosis. **D**, von Kossa staining.

toxicity and glomerulonephritis secondary to wound infection was also less likely with regards to urinalysis.

Minimal proteinuria was revealed by urinalysis, along with nondysmorphic erythrocytes and pyuria with leukocyte cast, all of which lead us to acute tubulointerstitial nephritis as the first diagnosis. However, after discontinuation of the offending drugs and treatment of urinary tract infection, no recovery was seen in kidney function; thus, we performed renal biopsy, and as mentioned above, tubulointerstitial nephritis with chronic changes was reported, which was not compatible with patient's history because he had had no any risk factors, sign and symptoms of chronic kidney failure. The patient was active and his kidneys were in normal size. Regarding the occurrence of extensive calcification in the interstitium and tubules with fibrosis and atrophy in a short period, acute phosphate nephropathy could have been a diagnosis. Thus, von Kossa staining was performed that showed extensive microcalcification in the interstitium and tubules, and then the study of slides under polarized microscopy showed negative birefringence that indicates calcium phosphate deposition.

The mechanism by which hyperphosphatemia would cause kidney injury is unknown. One hypothesis for explaining the pathogenesis is that transient hyperphosphatemia would lead to an increased intratubular phosphate concentration, resulting in the precipitation and tissue deposition of calcium phosphate, the results of which are luminal obstruction, direct tubular epithelial injury, and activation of the immune response.^{3,4} Hypovolemia can exacerbate this phenomenon as is seen in oral sodium phosphate ingestion. True or effective volume depletion would result in increased sodium chloride and water reabsorption in the proximal tubule. This effect is combined with ongoing water reabsorption in the descending limb of the loop of Henle raises the calcium phosphate product within the tubular lumen in the fluid presented to the ascending limb and distal tubule.⁵

The main pathologic characteristic of acute phosphate nephropathy is the extensive deposition of calcium phosphate in the tubular lumina, within tubular epithelial cells, and, less commonly, in the peritubular interstitium.⁶ Calcium phosphate deposits are distinguished from calcium oxalate

deposits by positive staining with the von Kossa staining and the absence of birefringence under polarized light.

The following potential risk factors for the development of acute phosphate nephropathy have been identified: phosphate dosing, chronic kidney disease, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, advanced age, diuretics, nonsteroidal anti-inflammatory agents, lithium, female sex, hypertension, and diabetes mellitus.⁷⁻¹⁹ Clinically, acute phosphate nephropathy is characterized by increases in serum creatinine that occur in asymptomatic patients and are documented days to months following oral sodium phosphate administration.

The diagnosis of phosphate nephropathy is supported by benign sediment on urinalysis and modest proteinuria. By definition, all patients with phosphate nephropathy should be normocalcemic, since hypercalcemia may also cause nephrocalcinosis. In this case, the lack of hypercalcemia and hypercalciuria and urinary calculi and acidic urine pH could decrease the probability of nephrocalcinosis. There are no reports of the use of imaging to demonstrate nephrocalcinosis in acute phosphate nephropathy. As a result, the diagnosis can be confirmed only by renal biopsy. In the present case, the cause of hyperphosphatemia was rhabdomyolysis. Also sodium bicarbonate infusion was used for correction of acidosis that may exacerbate the deposition of calcium phosphate in this patient; thus, we think that AKI is started by rhabdomyolysis and the continuous chronic changing was due to acute phosphate nephropathy.

The single most important preventive strategy is to identify patients who are at higher risk for the development of acute phosphate nephropathy and there is no specific treatment for established acute phosphate nephropathy. Accordingly, alkalinizing agents should probably not be used after the use of phosphosoda preparations and also be used with caution in treating or preventing uric acid nephropathy, since the threshold for calcium phosphate precipitation decreases in alkaline urine.²⁰ However, acute hemodialysis is likely to be beneficial in the patient who is diagnosed and still has marked hyperphosphatemia. Complete recovery of renal function is rare, these patients should be treated the same as others with chronic kidney disease.

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CONFLICT OF INTEREST

None declared.

REFERENCES

1. Markowitz GS, Perazella MA. Acute phosphate nephropathy. *Kidney Int.* 2009;76:1027.
2. Ori Y, Rozen-Zvi B, Chagnac A, et al. Fatalities and severe metabolic disorders associated with the use of sodium phosphate enemas: a single center's experience. *Arch Intern Med.* 2012;172:263.
3. Heher EC, Thier SO, Rennke H, Humphreys BD. Adverse renal and metabolic effects associated with oral sodium phosphate bowel preparation. *Clin J Am Soc Nephrol.* 2008;3:1494.
4. Hebert LA, Lemann J Jr, Petersen JR, Lennon EJ. Studies of the mechanism by which phosphate infusion lowers serum calcium concentration. *J Clin Invest.* 1966;45:1886.
5. Asplin JR, Mandel NS, Coe FL. Evidence of calcium phosphate supersaturation in the loop of Henle. *Am J Physiol.* 1996;270:F604.
6. Golub RW, Kerner BA, Wise WE Jr, et al. Colonoscopic bowel preparations—-which one? A blinded, prospective, randomized trial. *Dis Colon Rectum.* 1995;38:594.
7. Vanner SJ, MacDonald PH, Paterson WG, et al. A randomized prospective trial comparing oral sodium phosphate with standard polyethylene glycol-based lavage solution (Golytely) in the preparation of patients for colonoscopy. *Am J Gastroenterol.* 1990;85:422.
8. Barclay RL. Safety, efficacy, and patient tolerance of a three-dose regimen of orally administered aqueous sodium phosphate for colonic cleansing before colonoscopy. *Gastrointest Endosc.* 2004;60:527.
9. Hookey LC, Depew WT, Vanner SJ. A prospective randomized trial comparing low-dose oral sodium phosphate plus stimulant laxatives with large volume polyethylene glycol solution for colon cleansing. *Am J Gastroenterol.* 2004;99:2217.
10. Rostom A, Jolicoeur E, Dubé C, et al. A randomized prospective trial comparing different regimens of oral sodium phosphate and polyethylene glycol-based lavage solution in the preparation of patients for colonoscopy. *Gastrointest Endosc.* 2006;64:544.
11. Russmann S, Lamerato L, Motsko SP, et al. Risk of further decline in renal function after the use of oral sodium phosphate or polyethylene glycol in patients with a preexisting glomerular filtration rate below 60 ml/min. *Am J Gastroenterol.* 2008;103:2707.
12. Khurana A, McLean L, Atkinson S, Foulks CJ. The effect of oral sodium phosphate drug products on renal function in adults undergoing bowel endoscopy. *Arch Intern Med.* 2008;168:593.
13. Brunelli SM, Lewis JD, Gupta M, et al. Risk of kidney injury following oral phosphosoda bowel preparations. *J Am Soc Nephrol.* 2007;18:3199.
14. Gumurdulu Y, Serin E, Ozer B, et al. Age as a predictor of hyperphosphatemia after oral phosphosoda administration for colon preparation. *J Gastroenterol Hepatol.* 2004;19:68.
15. Hurst FP, Bohem EM, Osgard EM, et al. Association of oral sodium phosphate purgative use with acute kidney injury. *J Am Soc Nephrol.* 2007;18:3192.
16. Russmann S, Lamerato L, Marfatia A, et al. Risk of impaired renal function after colonoscopy: a cohort study in patients receiving either oral sodium phosphate or polyethylene glycol. *Am J Gastroenterol.* 2007;102:2655.
17. Ainley EJ, Winwood PJ, Begley JP. Measurement of serum electrolytes and phosphate after sodium phosphate colonoscopy bowel preparation: an evaluation. *Dig Dis Sci.* 2005;50:1319.
18. Heher EC, Thier SO, Rennke H, Humphreys BD. Adverse renal and metabolic effects associated with oral sodium phosphate bowel preparation. *Clin J Am Soc Nephrol.* 2008;3:1494.
19. Markowitz GS, Stokes MB, Radhakrishnan J, D'Agati VD. Acute phosphate nephropathy following oral sodium phosphate bowel purgative: an underrecognized cause of chronic renal failure. *J Am Soc Nephrol.* 2005;16:3389.
20. Desmeules S, Bergeron MJ, Isenring P. Acute phosphate nephropathy and renal failure. *N Engl J Med.* 2003;349:1006-7.

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