Kidney Research and Clinical Practice

Case Report

Does hypokalemia contribute to acute kidney injury in chronic laxative abuse?

Eun-Young Lee [1], Hyaejin Yoon [1], Joo-Hark Yi [1,*], Woon-Yong Jung [2], Sang-Woong Han [1], Ho-Jung Kim [1]

[1] Renal Division, Department of Internal Medicine, Hanyang University Guri Hospital, Guri, Korea
[2] Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

ABSTRACT

Prolonged hypokalemia from chronic laxative abuse is recognized as the cause of chronic tubulointerstitial disease, known as "hypokalemic nephropathy," but it is not clear whether it contributes to acute kidney injury (AKI). A 42-year-old woman with a history of chronic kidney disease as a result of chronic laxative abuse from a purging type of anorexia nervosa (AN-P), developed an anuric AKI requiring hemodialysis and a mild AKI 2 months later. Both episodes of AKI involved severe to moderate hypokalemia (1.2 and 2.7 mmol/L, respectively), volume depletion, and mild rhabdomyolysis. The histologic findings of the first AKI revealed the remnants of acute tubular necrosis with advanced chronic tubulointerstitial nephritis and ischemic glomerular injury. Along with these observations, the intertwined relationship among precipitants of recurrent AKI in AN-P is discussed, and then we postulate a contributory role of hypokalemia involved in the pathophysiology of the renal ischemia-induced AKI.

Introduction

The term "kaliopenic nephropathy" was introduced by Conn and Johnson [1] in 1956 to describe a distinct clinical entity characterized by the pathologic lesions of vacuolar tubulopathy and functional disorders such as impaired urine concentration in patients resulting from long-term potassium depletion. Since then, chronic laxative or diuretic abuse in patients of anorexia nervosa of purging type (AN-P) has been reported as a cause of chronic tubulointerstitial nephropathy due to hypokalemic nephropathy, sometimes leading to end-stage renal disease (ESRD) requiring renal replacement therapy including dialysis or renal transplantation [2–4]. There have been some reports of acute kidney injury (AKI) from unidentified causes in preexisting chronic kidney disease (CKD) due to hypokalemic nephropathy in the presence of chronic hypokalemia in AN-P [2,4,5].

Through the present case, we wish to advance a postulate that hypokalemia plays an important role in precipitating renal ischemia-induced AKI in the presence of other contributors of AKI.

Case report

A 42-year-old woman presented at the emergency department (ED) with chief complaints of anergy and progressive weakness of lower extremities for the past 10 days. She was emaciated with a body mass index of 14 kg/m^2 (weight 34 kg, height 155 cm). On further questioning, she confessed to having taken large amounts of three types of nonprescription laxatives (up to 50 tablets daily) for at least 10 years after the

* Corresponding author. Renal Division, Department of Internal Medicine, Hanyang University Guri Hospital, 249-1 Kyomoon-dong, Guri-si, Gyeonggi-do 471-701, Korea.
E-mail address: joohark@hanyang.ac.kr (J-H Yi).

birth of her second child. The laxative dosage was increased to almost 70 tablets a day over the previous month, and during this period she developed progressive loss of appetite. The laxatives contained bisacodyl, docusate sodium, sennoside calcium, *Lactobacillus acidophilus*, and carbenoxolone (glycyrrhetinic acid).

Vital signs in the supine position showed blood pressure 80/64 mmHg, heart rate 84/min, respiratory rate 24/min, and body temperature 37°C. She appeared severely volume depleted with poor skin turgor, dry oral mucosa, and shiny skin on both legs.

The initial laboratory data in the ED were as follows— complete blood examination: white blood cell count $12.1 \times 10^3/mm^3$, hemoglobin 9.0 g/dL, platelets $307 \times 10^3/mm^3$; serum chemistry: sodium 127 mmol/L, potassium 1.2 mmol/L, chloride 94 mmol/L, urea nitrogen 117 mg/dL, creatinine 11.7 mg/dL, calcium 6.3 mg/dL phosphate 8.5 mg/dL magnesium 2.2 mg/dL intact parathyroid hormone 80 pg/mL, creatine phosphokinase 3,371 units/L (30–180 units/L). Arterial blood gas on 4 L oxygen per minute showed pH 7.19, pO_2 163 mmHg, pCO_2 10.8 mmHg, HCO_3 4.2 mmol/L. Urinalysis yielded the following results: albumin (2+), occult blood (2+) with no red blood cells/high power field (HPF), pyuria 5–10/HPF with no bacteria.

A renal ultrasonogram on Day 3 showed 9.5 cm bilaterally with prominent medulla and nephrolithiasis in the left renal pelvis without hydronephrosis. In the supine position, the plasma renin activity and aldosterone level was 15.29 ng/mL/h (0.68–1.36 ng/mL/h) and 98.6 ng/dL (1.0–16 ng/dL), respectively. The serologic markers for glomerulonephritis were negative.

In the ED and the intensive care unit, 3 L of a half-normal saline mixed with KCl (60 mmol/L) and bicarbonate (100 mmol/L) were infused over 12 hours. However, the patient remained anuric (< 5 mL/h) with serum potassium of 1.7 mmol/L, and the electrocardiogram showed U waves, arterial pH 7.23, and blood bicarbonate 8.4 mmol/L. Subsequently, hemodialysis with 4 mmol/L of potassium in the dialysate was initiated and continued at a frequency of three times a week for 10 days until the patient passed urine (> 700–800 mL/d).

On Day 15, a kidney biopsy showed advanced chronic tubulointerstitial nephritis with some evidence of acute tubular necrosis (ATN). The predominant light microscopic lesions were moderate to severe residual atrophy or loss of tubules and scattered interstitial mononuclear cell infiltration (Fig. 1A). Also, focal tubular degenerative change and mild regenerative proximal tubules suggested ATN in the recovery phase, and a few nonatrophic tubular epithelial cells in the proximal tubule were focally enlarged and vacuolated. The glomeruli displayed ischemic changes such as wrinkling and thickening of the glomerular capillary walls but without advanced glomerular lesions (Fig. 1B). However, there was no evidence of juxtaglomerular hyperplasia or arteriolosclerosis. Immunofluorescence examinations showed no immunoglobulins or complements. Ultrastructurally, diffuse thickening of the glomerular basement membrane was noted with no electron dense deposits. Foot processes of podocytes showed moderate effacement (Fig. 1C).

On the day of discharge, the patient weighed 38 kg with serum potassium of 4.3 mmol/L and creatinine of 1.8 mg/dL. After intensive counseling from renal, psychiatric, social, and dietary consultants, she understood the seriousness of her condition, and agreed to refrain from laxative abuse.

However, on the second monthly follow-up at the outpatient renal clinic, her serum creatinine was increased to
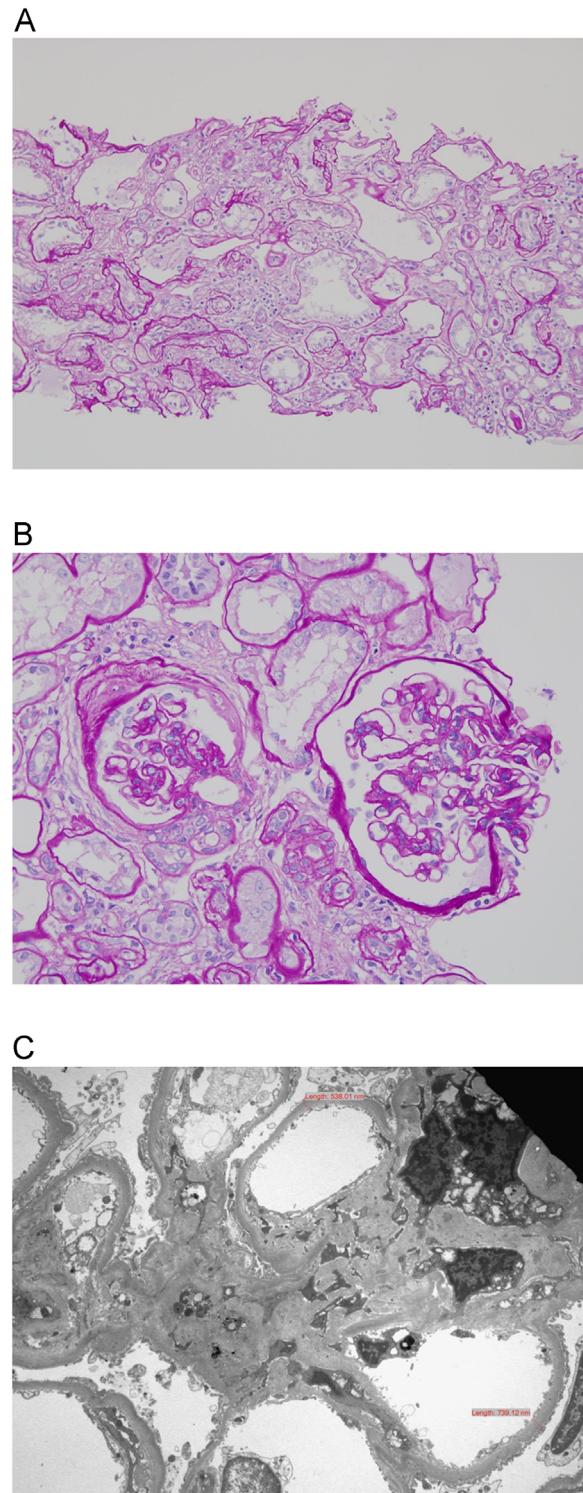
Figure 1. Renal histology. (A) The interstitium shows marked fibrosis with mild mononuclear cell infiltration. The tubules show various morphologic changes, including atrophy, detachment, and vacuolization of the epithelial cells, with nuclear atypia, which suggest tubular injury due to chronic damage (PAS, × 200). (B) The glomeruli show focal ischemic collapse (left) and segmental thickening of the glomerular basement membrane (right). The arterioles are unremarkable (PAS, × 400). (C) Electron microscopy shows diffuse thickening of the glomerular basement membrane, with average thickness of 574 nm. The foot processes are moderately effaced (× 3,500). PAS, periodic acid-Schiff.

2.7 mg/dL, which was also accompanied by decreased serum potassium to 2.7 mmol/L and body weight to 36 kg. On careful questioning, the patient admitted to resuming the intake of laxatives (about 50–70 tablets/d). She was again counseled about the serious renocardiac consequences of continued laxative abuse and the necessity of regular psychiatric follow-up for body image disorder. At the last follow-up 3 weeks later, her serum creatinine, serum potassium, and body weight had improved to 1.9 mg/dL, 4.1 mmol/L, and 38 kg, respectively.

Discussion

The present case, based on clinical presentation and pathological findings, describes two episodes of AKI due to severe renal ischemia from severe hypokalemia, volume depletion, and mild rhabdomyolysis, superimposed on preexisting CKD with hypokalemic nephropathy.

Our patient had two major potential contributing factors for AKI: severe volume depletion and rhabdomyolysis. The degree of rhabdomyolysis in our patient on the basis of creatine phosphokinase levels was quite mild and is unlikely to have caused AKI, whereas volume depletion was quite severe and could have precipitated AKI. By contrast, worsening hypokalemia and profound volume depletion as the predisposing factors for ischemic AKI appear to coexist in most AN-P cases. However, only one report of AN-P has considered the cause of AKI in detail; in that case, it was attributed to renal ischemia from profound volume depletion in the setting of hypokalemia (1.8–3.1 mmol/L), requiring transient hemodialysis with no response to initial intravenous volume replacement, as in the present case [5]. In a clinical study, 13 out of 40 patients with AN-P with severe to moderate hypokalemia (1.9–2.8 mmol/L) developed AKI, and this was attributed to hypovolemia alone [4]. Cremer and Bock [2] reported five episodes of AKI in three patients with AN-P, and did not note any apparent cause for AKI such as volume depletion or rhabdomyolysis, except for moderate hypokalemia (2.65–3.0 mm/L). In an animal study, hypokalemia could potentiate ischemic AKI [6].

It is unlikely that hypovolemia in AN-P is the only underlying cause for the pathogenesis of ischemic AKI. Other factors such as severe to moderate hypokalemia and/or rhabdomyolysis appear to lead to severe renal ischemia from intense intrarenal vasoconstriction and decreased activation of the neurohumoral system responsible for intrarenal vasodilation, a recognized factor in the pathophysiology of ischemic AKI [7]. In fact, one case report in a laxative abuser has suggested volume depletion and hypokalemia-related tubular lesions as causes of the anuric AKI, and termed it "hypokalemia-induced acute renal failure" [8]. Patients with long-term AN-P who are diuretic or laxative abusers are constantly at a risk of chronic potassium deficiency, either owing to direct loss of potassium by the renal and/or extrarenal route or to high levels of angiotensin II and aldosterone as a result of activation of the renin–angiotensin–aldosterone system secondary to hypovolemia following the loss of water and salt induced by purging combined with restricted food intake. Therefore, the hypokalemic nephropathy and AKI in chronic laxative abusers with AN-P appear to involve two major factors—hypokalemia and hypovolemia. These result in renal ischemia as follows: (1) The hypokalemia stimulates increased ammoniagenesis, which in turn activates the alternative complement pathway

releasing proinflammatory cytokines and profibrotic molecules.
(2) The hypokalemia also stimulates the production of vasoactive mediators, resulting in increased vasoconstrictor stimuli (endothelin-1, thromboxane B_2, angiotensin-converting enzyme, angiotensin II) and reduced vasodilatory mediators such as prostaglandin E_2 and endothelium-derived relaxing factor. (3) The hypovolemia causes renal ischemia directly, with activation of the renin–angiotensin–aldosterone system [9–13].

In the present case, the most likely cause of the intermittent or recurrent AKI was renal ischemia due to intrarenal vasoconstriction caused by the worsening of hypokalemia and hypovolemia. However, the preexisting CKD due to longstanding hypokalemic nephropathy was also an important factor in the patient's recurrent episodes of AKI. The histological findings from the kidney biopsy performed on Day 15 showed ATN with focal tubular degenerative change including mild regenerative and vacuolar proximal tubules, and prominent chronic tubulointerstitial nephritis combined with diffuse ischemic glomerular changes such as wrinkling and thickening of the glomerular basement membrane (Figs. 1A–1C). The clinicopathological findings compatible with hypokalemic nephropathy showed that tubulopathy alone may lead to CKD as a result of tubulointerstitial fibrosis, as in the renal fibrosis in CKD due to glomerulopathy. Our findings also support a contributory role of AKI in the progression of CKD in patients with AN-P involving a vicious cycle of the preexisting CKD and repeated episodes of AKI. Underlying CKD is a major predisposing factor for AKI, and recurrent AKI superimposed on CKD may increase the rate of loss of the remaining nephron mass [14].

In conclusion, episodes of worsening hypokalemia in AN-P could play an important role in the progression of the preexisting CKD with hypokalemic nephropathy, as suggested in a recent study that shows hypokalemia in CKD to be a risk factor for progression to ESRD [15]. Health providers involved in the care of patients with hypokalemic nephropathy, particularly patients with AN-P, should address potassium depletion and hypovolemia as well as offer intensive counseling to encourage the patients to abstain from purgative drug abuse.

Conflict of interest

All authors declare no conflict of interest.

Acknowledgments

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