Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.4217-19
Intern Med 59: 1659-1663, 2020
http://internmed.jp

【 CASE REPORT 】

Acute Kidney Injury with Hemolysis after Glycerin Enema-induced Rectal Injury in a Patient with Type 2 Diabetes

Ryosuke Hayashida, Kyoichiro Tsuchiya, Suguru Nakamura, Noriyuki Harima, Masashi Ichijo, Fumihiko Furuya and Kenichiro Kitamura

Abstract:
A 66-year-old man with type 2 diabetes was admitted for glycemic control and weight loss. The rectal mucosa was unfortunately injured during glycerin enema administration in preparation for colonoscopy, after which dark red urine and renal dysfunction were observed. Considering the clinical diagnosis of glycerol-induced hemolysis and acute kidney injury, intravenous hydration and haptoglobin administration were started, which successfully treated the dark red urine and renal dysfunction. This case highlights the importance of appropriate glycerin enema administration and emphasizes the need to recognize glycerol-induced hemolysis and acute kidney injury as complications of glycerin enemas. This case also provides insight into glycerol-induced hemolysis and acute kidney injury as complications of glycerin enemas.

Key words: glycerin enema hemolysis, hemolysis, acute kidney injury

(Intern Med 59: 1659-1663, 2020)
(DOI: 10.2169/internalmedicine.4217-19)

Introduction

Glycerin enemas have been widely used in daily clinical practice as well as in home care situations. This medical procedure is generally regarded as safe and is not believed to cause severe complications. However, glycerol has been known to induce hemolysis and acute kidney injury (AKI), given its high osmolality and molecular weight. Since the 1970s, cases of intravascular hemolysis and/or AKI caused by intravenous glycerin infusion have been reported (1). However, intravascular hemolysis and/or AKI after inappropriate glycerin enema administration have rarely been recognized or reported in English publications.

We herein report a case involving AKI in a patient with type 2 diabetes following rectal injury during glycerin enema administration. This case provides insight into glycerol-induced hemolysis and AKI as complications of glycerin enema.

Case Report

A 66-year-old man with type 2 diabetes was admitted to the University of Yamanashi Hospital (Yamanashi, Japan) due to poor glycemic control. The patient unintentionally lost 7 kg of body weight over 3 months, and his HbA1c and blood glucose concentrations on admission were 14.6% and 227 mg/dL, respectively (Table 1). He had maintained normal serum creatinine concentrations for at least the past 1.5 years and had no positive dipstick test for urinary protein or blood. The patient had simple diabetic retinopathy but no history of diabetic neuropathy, nephropathy, macroangiopathy, or hemorrhoids.

The urinary albumin excretion and estimated glomerular filtration rate at admission were 9.6 mg/gCr and 108 mL/min/1.73 m^2, respectively. After admission, glycemic control was started through multiple daily injections of insulin glargine and lispro, while detailed examinations concerning his body weight reduction were planned. Abdominal ultrasonography and computed tomography (CT) revealed no

Third Department of Internal Medicine, Interdisciplinary Graduate School of Medicine and Engineering, University of Yamanashi, Japan
Received: November 19, 2019; Accepted: February 26, 2020; Advance Publication by J-STAGE: April 9, 2020
Correspondence to Dr. Kyoichiro Tsuchiya, tsuchiyak@yamanashi.ac.jp

Table 1. Laboratory Data on Admission and at Onset.

	Adm.	Onset			Adm.	Onset	
[Biochemistry]				Cl	99	104	mEq/L
T-Bil	1.2	2.7	mg/dL	[Hematology]			
ALP	204	190	U/L	WBC	3,390	8,020	/μL
γ-GTP	22	25	U/L	RBC	460	457	$\times 10^4$/μL
LDH	150	490	U/L	Hb	14.8	14.8	g/dL
AST	15	54	U/L	Plt	17.5	14.7	$\times 10^4$/μL
ALT	18	42	U/L	[Urine]			
CK	53	634	U/L	Pro	(-)	(2+)	
BUN	13.9	16	mg/dL	Blood	(-)	(3+)	
Cr	0.57	1.18	mg/dL	Bil	(-)	(-)	
CRP	≤0.10	≤0.10	mg/dL	UB	(+-)	(+-)	
Na	136	140	mEq/L	RBC	<1/H	10-19	/HPF
K	3.7	4.1	mEq/L				

adm: admission, T-Bil: total bilirubin, ALP: alkaline phosphatase, γ-GTP: γ-glutamyl transpeptidase, LDH: lactate dehydrogenase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, BUN: blood urea nitrogen, Cr: creatinine, CRP: C-reactive protein, Na: sodium, K: potassium, Cl: chloride, WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, Ht: hematocrit, Plt: platelet, Pro: protein, Bil: bilirulin, UB: urobilinogen

evidence explaining his weight loss. Furthermore, carcinoembryonic antigen and CA19-9 values were 8.8 and 1.26 ng/mL, respectively. Although fecal occult blood tests were negative, total colonoscopy was scheduled on the 9th day of hospitalization. Immediately after a nurse administered 120 mL of a 50% glycerin enema as bowel preparation, the patient complained of acute anal pain with melena. Emergency colonoscopy revealed two lacerations in the edematous mucosa below the anal dentate line (Fig. 1A). Emergency contrast-enhanced abdominal CT showed contrast effect in the rectal mucosa without free air around the rectum (Fig. 1B), suggesting mucosal injury without perforation. The patient began fasting, and antibiotic treatment (TAZ/PIPC) was started. Despite normal vital signs, dark red urine was observed 5 hours after the enema. A urine dipstick test for blood was strongly positive (3+), accompanied by a relatively small number of erythrocytes (10-19/HPF). The test for bilirubin or urobilinogen was not positive, and no schistocyte was observed. A blood analysis showed mild renal dysfunction, indicated by elevated serum creatinine concentrations (0.57 to 1.18 mg/dL) with increased serum total bilirubin, lactate dehydrogenase (LDH), potassium, and aspartic aminotransferase (AST) levels (Table 1). Although serum creatine kinase (CK) concentrations were also increased, no apparent symptoms or electrocardiogram changes suggesting the onset of ischemic heart disease were noted. The serum haptoglobin and myoglobin levels were not assessed at the onset. Based on the aforementioned clinical information, a diagnosis of hemolytic renal dysfunction caused by migration of a glycerin enema into the blood after rectal injury was suspected.

Intravenous saline and bicarbonate Ringer's solution (3,000 mL/12 h) as well as haptoglobin (4,000 IU/day for 1 day) were immediately administered to prevent further complications associated with hemolysis (Fig. 2A). Approximately 24 hours after the onset, the urine dipstick test for blood was negative (Fig. 2B), serum haptoglobin level was 78 mg/dL, and serum and urinary myoglobin levels were 228.8 and 62 ng/mL, respectively (Table 2). On the 3rd day after onset, a blood test showed normalization of serum creatinine, AST, potassium, and LDH concentrations, with the serum CK concentration subsequently normalizing on the 4 th day after the onset. Enhanced abdominal CT on the 6th day after the onset revealed little contrast effect, suggesting improvement in the rectal mucosa injury. Thereafter, oral intake was resumed, and TAZ/PIPC was discontinued. The patient was finally discharged on the 12th day after the onset, and his renal function has remained normal ever since.

Discussion

In 1974, the first three human cases of intravascular hemolysis and/or AKI caused by intravenous glycerin infusion were reported (1). Thereafter, reports were published showing that the use of low-concentration (10%) glycerol solutions containing small amounts of fructose could attenuate hemolysis in humans by preventing membrane dehydration of erythrocytes (2, 3). In contrast, glycerin enemas usually contain high (50%) concentrations of glycerol without fructose. Taken together, these previous findings suggest that glycerol-induced hemolysis and/or AKI is more likely to occur through inappropriate glycerin enema administration than through intravenous glycerol agents.

At the onset in the present case, we were unable to check the serum haptoglobin level and did not observe any anemia or schistocytes. Therefore, our findings might not have indicated a definitive diagnosis of hemolysis. However, based on all of the clinical information, including rectal injury by

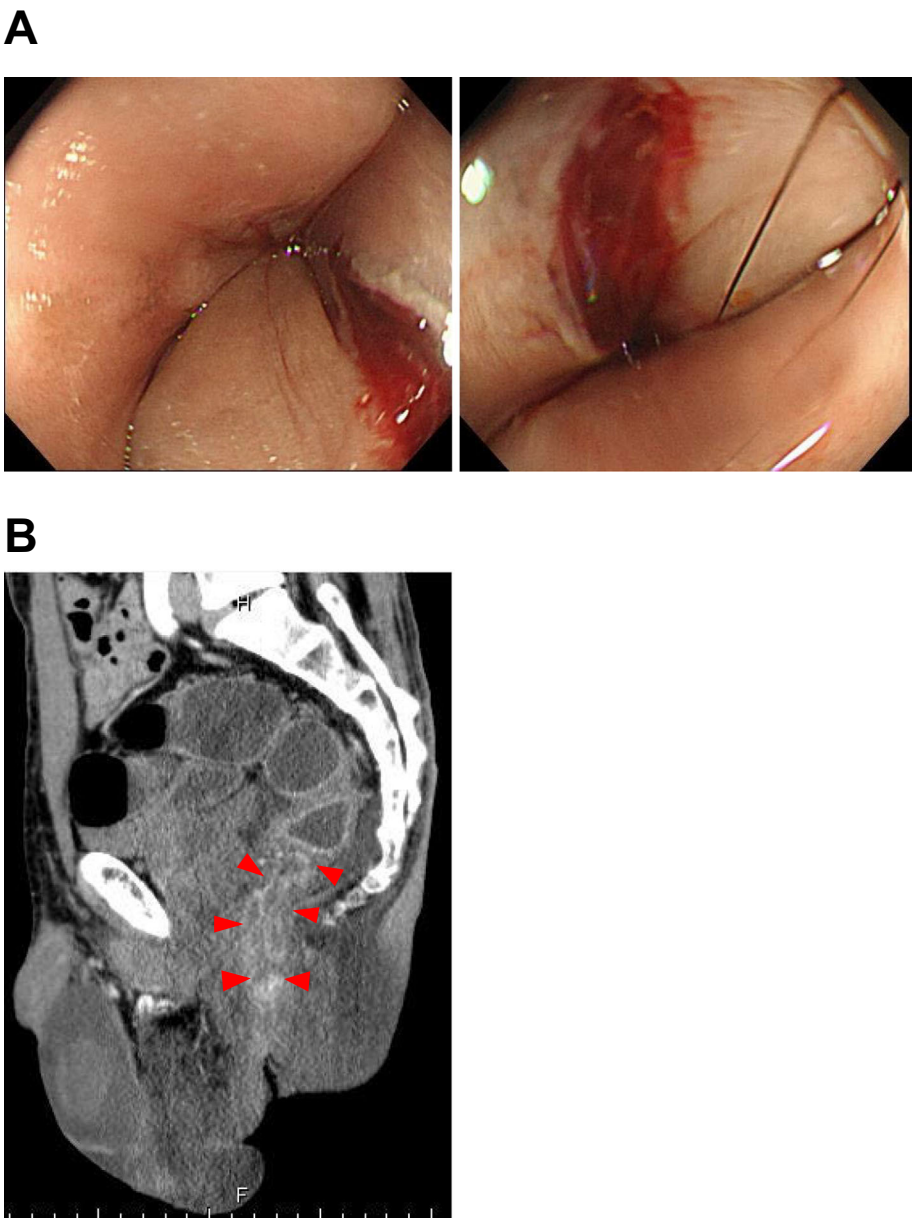

Figure 1. Colonoscopy and computed tomography (CT). (A) Colonoscopy revealed two lacerations in the edematous mucosa below the anal dentate line. (B) Abdominal CT revealed that contrast effect (arrowheads) was limited within the mucosal lesion.

glycerin enema, we considered hemolysis to be the most likely diagnosis to begin treatment with hydration and haptoglobin. Indeed, the clinical course after treatment was consistent with the diagnosis.

Glycerin is rapidly metabolized to carbon dioxide and glycogen by glycolysis, and the elimination half-life of glycerin in serum is consequently about 0.18-0.87 hours (4). This suggests that glycerol-induced hemolysis does not last for a long time unless the migration of glycerin continues, and not all typical laboratory findings of hemolysis may be observed. Furthermore, hydration and haptoglobin treatment were immediately started in the present case, which might have partly masked some findings of AKI.

Although the significance and efficacy of haptoglobin treatment for glycerin enema-induced hemolysis remains unclear, it may prevent the progression to hemodialysis; from 1979 to 2017, 15 cases of hemolysis following glycerin enemas were reported in case series and reports in Japanese (5-7). Apparent rectal injury and hemorrhoids were observed in 10 and 6 cases, respectively. While one of seven patients treated with haptoglobin underwent hemodialysis, two of seven patients who did not receive haptoglobin underwent the same treatment. Fortunately, no deaths were observed in any of those cases. Haptoglobin treatment might thus have helped attenuate the progression of AKI in the present case.

Glycerol-induced AKI involves at least two mechanisms: hemolysis and rhabdomyolysis. After hemolysis is induced by increases in intracellular osmolality in erythrocytes, intracellular hemoglobin dissociates into heme and globin. The liberated heme may injure the kidney via tubular obstruction, direct injury of tubular epithelial cells, or vasoconstric-

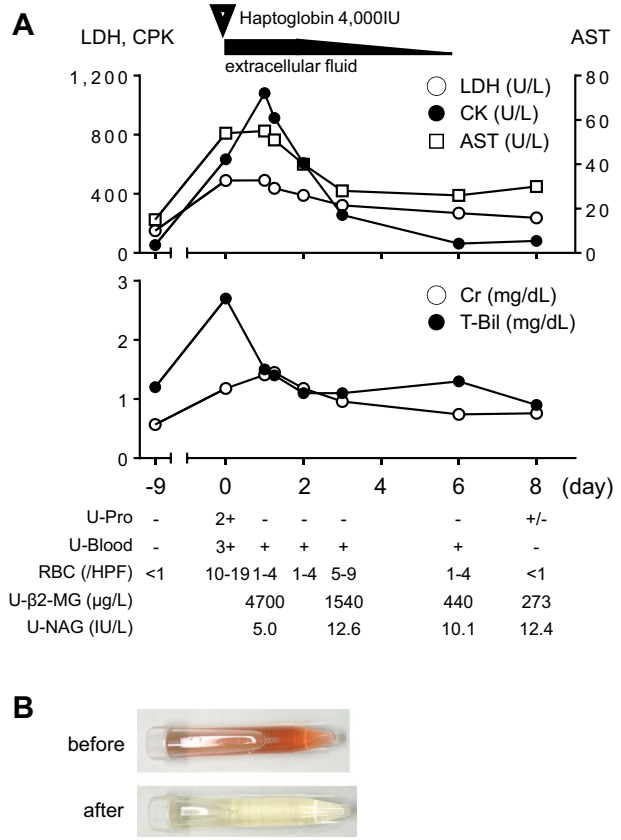

Figure 2. **Clinical course. (A) The clinical course. Days -9 and 0 indicate admission and onset, respectively. (B) Appearances of urine before (left) and 24 h after (right) haptoglobin administration. U-β2-MG: urinary beta-2 microglobulin, U-NAG: urinary N-acetyl-beta-glucosaminidase**

tion (8-10). In addition, glycerin is usually injected into the muscle to cause rhabdomyolysis in experimental animal models of glycerol-induced AKI. This results in the leakage of intracellular muscle contents, including lactate dehydrogenase, myoglobin, glutamic oxalacetic transaminases, and CK, into the circulation. These substances also induce tubular obstruction and renal vasoconstriction (11-13). In the present case, the increase in the serum creatinine level was transient, suggesting that vasoconstriction was more likely the major pathogenesis than renal intrinsic AKI. In the present case, free heme might also have caused direct injury of the proximal tubular epithelial cells, represented as increased urinary beta-2 microglobulin and N-acetyl-beta-glucosaminidase levels. However, hydration and the prompt administration of haptoglobin might have prevented sustained renal failure.

In the present case, increased serum and urinary myoglobin levels, despite being assessed 24 hours after the onset, may have contributed to the pathogenesis of AKI, at least in part. However, glycerol migration into the bloodstream was considered the main cause of the hemolysis. Despite using animal data for calculations, a previous report found that only 1.2 mL of intravenous 50% glycerin was sufficient to cause hemolysis in a 50 kg human (14). Although the exact volume of migrated glycerol in the present patient remains unknown, a sufficient volume was likely to have migrated into the bloodstream and induced hemolysis. The relatively mild subsequent increase in the serum CK concentration suggests that myoglobin contributed less to the pathogenesis of AKI than glycerol-induced hemolysis.

Table 2. **Serum Haptoglobin, Serum Myoglobin, and Urinary Myoglobin Levels 24 h after Onset.**

Serum haptoglobin	78.0 mg/dL	(15-116)
Serum myoglobin	228.8 ng/mL	(≤54.9)
Urinary myoglobin	62.0 ng/mL	(≤10)

Normal range shown in parentheses.

The present patient had poorly controlled type 2 diabetes, a proinflammatory state characterized by increased levels of C-reactive protein and proinflammatory cytokines as well as monocyte activation (15). In addition to inflammatory bowel diseases, studies have shown that patients with diabetes exhibit digestive tract inflammation and increased intestinal vulnerability (16, 17). Mucosal vulnerability associated with diabetes may have contributed to the rectal injury following forcible insertion, which then promoted the glycerol-induced hemolysis in the present case.

In conclusion, we reported a case of AKI with hemolysis after glycerin enema-induced rectal injury in a patient with type 2 diabetes. The present case highlights the importance of appropriate glycerin enema administration and emphasizes the need to recognize glycerol-induced hemolysis and AKI as complications of glycerin enemas.

Written informed consent was obtained from the patient for publication of this Case Report and any accompanying images. A copy of the written consent is available upon request.

The authors state that they have no Conflict of Interest (COI).

References

1. Hagnevik K, Gordon E, Lins LE, Wilhelmsson S, Forster D. Glycerol-induced haemolysis with haemoglobinuria and acute renal failure. Report of three cases. Lancet **1**: 75-77, 1974.
2. Kumana CR, Yu YL, Chang CM, Kou M, Wei D. Glycerol infusion rates warrant caution. Stroke **22**: 1608, 1991.
3. Tsubokawa T, Katayama Y, Ishii S. Fructose-added glycerol (Glyceol) for therapy of elevated intracranial pressure: analysis of the side effects of long-term administration in a multi-institutional trial. Neurol Res **11**: 249-252, 1989.
4. Tibbling G. Glycerol turnover in hyperthyroidism. Clin Chim Acta **24**: 121-130, 1969.
5. Nanami T, Shimada N, Honda Y, Ishii N, Kurihara A, Sugimoto M. A case of rectal damage and hemolysis caused by glycerin enema. J Jpn Surg Assoc **69**: 1442-1446, 2008 (in Japanese).
6. Okawa T, Furuta T, Kanagawa T, Kobatake T, Nogami H. Rectal perforation and fistulae secondary to a glycerin enema, treated with conservative therapy-two case reports-. J Jpn Surg Assoc **78**: 1041-1049, 2017 (in Japanese).

7. Ohigashi Y, Otsuki K, Yabuuchi H, Matsumoto M, Nakamoto T, Hokuto D. A case of hemolytic renal dysfunction caused by rectal injury resulting from glycerin enema. J Jpn Surg Assoc **77**: 1171-1176, 2016 (in Japanese).
8. Zager RA. Rhabdomyolysis and myohemoglobinuric acute renal failure. Kidney Int **49**: 314-326, 1996.
9. Holt S, Moore K. Pathogenesis of renal failure in rhabdomyolysis: the role of myoglobin. Exp Nephrol **8**: 72-76, 2000.
10. Zager RA, Burkhart KM, Conrad DS, Gmur DJ. Iron, heme oxygenase, and glutathione: effects on myohemoglobinuric proximal tubular injury. Kidney Int **48**: 1624-1634, 1995.
11. Vanholder R, Sever MS, Erek E, Lameire N. Rhabdomyolysis. J Am Soc Nephrol **11**: 1553-1561, 2000.
12. Ayer G, Grandchamp A, Wyler T, Truniger B. Intrarenal hemodynamics in glycerol-induced myohemoglobinuric acute renal failure in the rat. Circ Res **29**: 128-135, 1971.
13. Kurtz TW, Maletz RM, Hsu CH. Renal cortical blood flow in glycerol-induced acute renal failure in the rat. Circ Res **38**: 30-35, 1976.
14. Takeda T. Verifiable research on hemoglobinuria induced in rats by glycerin enemas. Jpn J Nurs Art Sci **5**: 45-50, 2006 (in Japanese).
15. Lee YS, Wollam J, Olefsky JM. An integrated view of immunometabolism. Cell **172**: 22-40, 2018.
16. Zhong HJ, Yuan Y, Xie WR, Chen MH, He XX. Type 2 diabetes mellitus is associated with more serious small intestinal mucosal injuries. PLoS One **11**: e0162354, 2016.
17. Winer DA, Luck H, Tsai S, Winer S. The intestinal immune system in obesity and insulin resistance. Cell Metab **23**: 413-426, 2016.