【 CASE REPORT 】

Metformin-associated Lactic Acidosis Induced by Excessive Alcohol Consumption

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Abstract:

A 65-year-old man with type 2 diabetes who was being treated with metformin developed lactic acidosis following excessive alcohol consumption. While an impaired renal function is a major risk factor for metformin-associated lactic acidosis (MALA), the patient's basal renal function was normal. Alcohol misuse reduces lactate clearance by utilizing nicotinamide adenine dinucleotides for ethanol oxidation, thereby promoting vulnerability to MALA. Nevertheless, as MALA in individuals with a normal renal function is extremely rare, the clinical picture of alcohol-induced MALA is unclear. We delineate the clinical picture and discuss the pathogenesis of alcohol-induced MALA based on our experience and previous case reports.

Key words: lactic acidosis, metformin, alcohol

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Introduction

Metformin is the most commonly prescribed oral antihyperglycemic agent for the treatment of diabetes mellitus worldwide and is considered the first-line therapy for newly diagnosed type 2 diabetes mellitus by the American Diabetes Association and European Association for the Study of Diabetes (1). With over 60 years of real-world global clinical experience, metformin is generally regarded as effective and safe unless there are contraindications (2, 3).

Metformin-associated lactic acidosis (MALA) is a rare but serious adverse effect of metformin, with an estimated incidence of <10 events per 100,000 patient-years of exposure and a mortality rate of 30-50% (4). MALA is generally precipitated by metformin accumulation due to an impaired renal function (4). In contrast, acute alcohol intoxication is associated with impaired hepatic lactate clearance, which may increase the risk of lactic acidosis (5). However, since MALA is extremely rare in patients with a normal renal function (6), a detailed clinical picture of alcohol-induced MALA is unknown.

We herein report a case of alcohol-induced MALA in a patient with a normal renal function. Furthermore, we describe the clinical picture and discuss the pathogenesis of alcohol-induced MALA based on our experience and previous reports.

Case Report

A 65-year-old Japanese man was transported to the emergency room with the chief complaint of vomiting. His medical history included type 2 diabetes mellitus, alcoholic hepatitis, and chronic pancreatitis. There was no history of chronic kidney disease, and the outpatient serum creatinine prior to the visit was 0.9 mg/dL [estimated glomerular filtration rate (eGFR) 66 mL/min/1.73 m^2]. The duration of type 2 diabetes was more than seven years, and it was complicated by microalbuminuria and distal symmetric polyneuropathy. The presence of retinopathy was uncertain.

The patient was prescribed insulin degludec (6.5 unit once daily), metformin (500 mg twice daily), sitagliptin (50 mg once daily), mitiglinide (10 mg twice daily), and voglibose (0.3 mg thrice daily). The patient had temporarily refrained from consuming alcohol six years ago during his hospitalization for pancreatitis but resumed the habit shortly thereafter. Unfortunately, he did not report persistent alcohol consumption by his physician. The patient had been on leave from work for 1 week because of low back pain syndrome, and his alcohol intake increased 2-fold compared to his nor-

mal habit (from 130 g/day to 260 g/day) during this period. The day before the visit, the patient developed anorexia but continued to consume ethanol. He continued to drink on the day of the visit and experienced multiple episodes of vomiting from midday onwards. The patient visited the emergency room on the evening of the same day.

A clinical examination revealed tachycardia (122 beats per minute) with a normal blood pressure of 117/71 mmHg. The respiratory rate was 24 breaths per minute, and transcutaneous oxygen saturation was 98% on room air. His body mass index was 17.3 kg/m^2 (height, 170 cm; body weight, 50 kg). A physical examination revealed no signs of mucosal dryness. The abdomen was flat and soft with no tenderness, and the liver and spleen were not palpable.

Laboratory tests revealed acidemia (pH, 6.97) with a low serum bicarbonate level (7.9 mmol/L) and marked hyperlactatemia (serum lactate, 30.0 mmol/L). The concentration ratio of lactate to pyruvate was also markedly elevated (lactate, 217.7 mg/dL; pyruvate, 3.73 mg/dL; and lactate/pyruvate ratio, 58.4). However, the serum ketone level was mildly elevated (serum ketone, 2.1 mmol/L). Moderate renal impairment (serum creatinine, 1.40 mg/dL; eGFR, 40 mL/min/1.73 m^2) and high transaminase levels with aspartate aminotransferase predominance (aspartate aminotransferase, 117 U/L; alanine aminotransferase, 34 U/L) were also observed. The prothrombin time was not prolonged (prothrombin time-international normalized ratio, 0.88), and the serum albumin level was within the normal range (serum albumin, 4.4 g/dL). Thus, there was no apparent decrease in the hepatic synthetic capacity. Hematocrit and urea nitrogen values were within normal ranges (hematocrit, 47.9%; urea nitrogen, 16 mg/dL), and intravascular dehydration was not evident (Table 1).

Based on low blood pH (<7.35) and elevated lactate levels (>5.0 mmol/L), the patient was diagnosed with lactic acidosis (7). Bedside echocardiography showed that the left ventricular contractility was preserved, and the inferior vena cava did not collapse. Based on physical, laboratory, and ultrasound findings, the patient did not have circulatory failure or tissue hypoxia (type B lactic acidosis) and was taking metformin; thus, we considered MALA (7).

As circulation was preserved, and the urine output was maintained, the patient was infused with a crystalloid solution under careful monitoring. After the initiation of infusion, serum lactate levels continued to decrease. Metabolic acidosis resolved on day 2 of hospitalization, and serum lactate levels normalized on day 3 (Figure). Abdominal ultrasonography was performed after the patient's general condition had stabilized. No morphological changes were observed in the liver, suggestive of cirrhosis. The patient was discharged on day 17. The prescriptions at discharge were insulin glargine (10 units once daily), insulin lispro (10 units 3 times daily before each meal), and sitagliptin (50 mg once daily).

Discussion

We herein report a case of MALA that was induced by excessive alcohol consumption. Although the patient regularly consumed large amounts of alcohol, no evidence of cirrhosis or an impaired liver function was observed. In addition, the basal renal function was normal.

Although metformin use is not contraindicated in the US or other countries, alcohol consumption may increase the risk of lactic acidosis (4, 5). However, how much alcohol intake leads to MALA development is unclear. Therefore, we compiled cases of alcohol-induced MALA with no baseline renal impairment and documented amounts of alcohol intake. A literature search using the search terms 'alcohol' and 'metformin-associated lactic acidosis' in PubMed, Google Scholar, and Ichushi-Web (Japanese database of medical articles) identified four case reports (Table 2) (6, 8-10).

In patients taking metformin at a regular dose (<2,250 mg/day in Japan), alcohol consumption was >100 g/day. The amount of alcohol consumed was based on self-report. Therefore, it is possible that the patients consumed an even higher amount of ethanol than that presented in the studies. Nevertheless, it seems advisable to assume a risk of MALA when the amount of alcohol consumed exceeds 100 g/day. Therefore, the rate of alcohol consumption is important. In one study, patients with diabetes mellitus taking 3,000 mg/day of metformin ingested 30 g of ethanol in 1 min, and their blood lactate levels increased to 4 mmol/L after 1 h (11). Therefore, it is possible that even a relatively small amount of ethanol consumed in a short period may lead to the development of MALA.

None of the patients presented in Table 2 died. The prognosis of patients with MALA has been suggested to be associated with the severity of the underlying diseases (4). Thus, the mortality rate of alcohol-induced MALA in relatively young patients without chronic kidney disease or cirrhosis may be lower than the overall mortality rate of MALA.

Interestingly, the majority of the patients with alcohol-induced MALA presented in Table 2 consumed alcohol until the day of the onset. This is in contrast to alcoholic ketoacidosis (AKA), which often occurs 24-72 h after alcohol cessation and is characterized by low or undetectable blood alcohol levels (12).

The difference in onset timing may reflect differences in pathophysiology. Ethanol metabolism involves the reduction of nicotinamide adenine dinucleotide (NAD) to dihydronicotinamide dinucleotide (NADH). The increased NADH/NAD ratio converts pyruvate metabolism to lactate and inhibits gluconeogenesis (13). Indeed, in our patient, the lactate/pyruvate ratio, which is proportional to the cytoplasmic NADH/NAD ratio, was markedly elevated to 58.4 (normal range: 4-10) (14). Finally, metformin inhibits hepatic gluconeogenesis in a redox-dependent manner, which may lead to the development of lactic acidosis during acute alcohol intoxication (15).

Table 1. Laboratory Findings.

| Laboratory test	Results	Reference range
pH	6.966	7.35-7.45
pCO$_2$ (mmHg)	23.0	35-48 mmHg
pO$_2$ (mmHg)	105.0	83-108 mmHg
HCO$_3$ (mmol/L)	7.9	21-28 mmol/L
AG (mmol/L)	45.7	10-20 mmol/L
Lactate (mmol/L)	30.0	0.5-1.6 mmol/L
Lactate (mg/dL)	217.7	3.0-17.0 mg/dL
Pyruvate (mg/dL)	3.73	0.30-0.94 mg/dL
Blood ketone (mmol/L)	2.1	<0.6 mmol/L
AAc (mmol/L)	0.925	<0.055 mmol/L
3-HBA (mmol/L)	2.171	<0.085 mmol/L
PT-INR	0.88	0.9-1.1
WBC (×100 /μL)	104.7	33-86×100 /μL
Hb (g/dL)	15.4	11.6-14.8 g/dL
Plt (×10,000 /μL)	16.4	15.8-34.8×10,000 /μL
ALB (g/dL)	4.4	4.1-5.1 g/dL
BUN (mg/dL)	16	8-20 mg/dL
Cre (mg/dL)	1.40	0.46-0.79 mg/dL
eGFR (mL/min/1.73 m^2)	40.5	>90 mL/min/1.73 m^2
UA (mg/dL)	7.5	3.7-7.8 mg/dL
Na (mEq/L)	135.9	138-145 mEq/L
K (mEq/L)	5.64	3.6-4.8 mEq/L
Cl (mEq/L)	85.5	101-108 mEq/L
AST (U/L)	117	13-30 U/L
ALT (U/L)	34	7-23 U/L
LDH (U/L)	348	124-222 U/L
ALP (U/L)	114	38-113 U/L
γ-GTP (U/L)	190	9-32 U/L
Total Bil (mg/dL)	0.54	0.40-1.50 mg/dL
AMY (U/L)	155	44-132 U/L
CK (U/L)	135	41-153 U/L
Glu (mg/dL)	230	73-109 mg/dL
HbA1c (%)	7.9	4.9-6.0 %
CRP (mg/dL)	0.33	0.00-0.14 mg/dL

3-HBA: 3-hydroxybutyric acid, AAc: acetoacetate, AG: anion gap, ALB: albumin, ALP: alkaline phosphatase, ALT: alanine transaminase, AMY: amylase, AST: aspartate aminotransferase, Bil: bilirubin, BUN: blood urea nitrogen, CK: creatine kinase, Cl: chloride, Cre: creatinine, CRP: C-reactive protein, eGFR: estimated glomerular filtration rate, γ-GTP: γ-glutamyl transferase, Glu: glucose, Hb: hemoglobin, HbA1c: hemoglobin A1c, HCO$_3$: bicarbonate, K: potassium, LDH: lactate dehydrogenase, Na: sodium, pCO$_2$: carbon dioxide partial pressure, Plt: platelet, pO$_2$: oxygen partial pressure, PT-INR: prothrombin time and international normalized ratio, UA: uric acid, WBC: white blood cell

Once ethanol ingestion ceases, the hepatic NADH/NAD ratio returns to normal, allowing gluconeogenesis to normalize. This reduces the levels of circulating lactic acid and oxaloacetate, which are gluconeogenic substrates. The depletion of oxaloacetate due to increased gluconeogenesis predisposes ketogenesis, as this substrate is essential for acetyl-CoA to enter the citric acid cycle (13, 16). This mechanism is believed to be the reason for AKA development a few days after the discontinuation of alcohol intake.

One factor contributing to alcohol-induced MALA is the inhibition of gluconeogenesis and reduced lactate clearance.

In contrast, in AKA, one of the contributing factors is the reversal of gluconeogenesis inhibition, which leads to oxaloacetate depletion. Considering the incompatible pathophysiologies, the likelihood of the simultaneous onset of alcohol-induced MALA and AKA appears to be low. In cases where ketoacidosis complicates alcohol-induced MALA, it may be important to consider causes of ketoacidosis other than AKA, such as diabetic ketoacidosis.

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

Extracellular fluid 1,500 mL

Extracellular fluid 2,500 mL/day
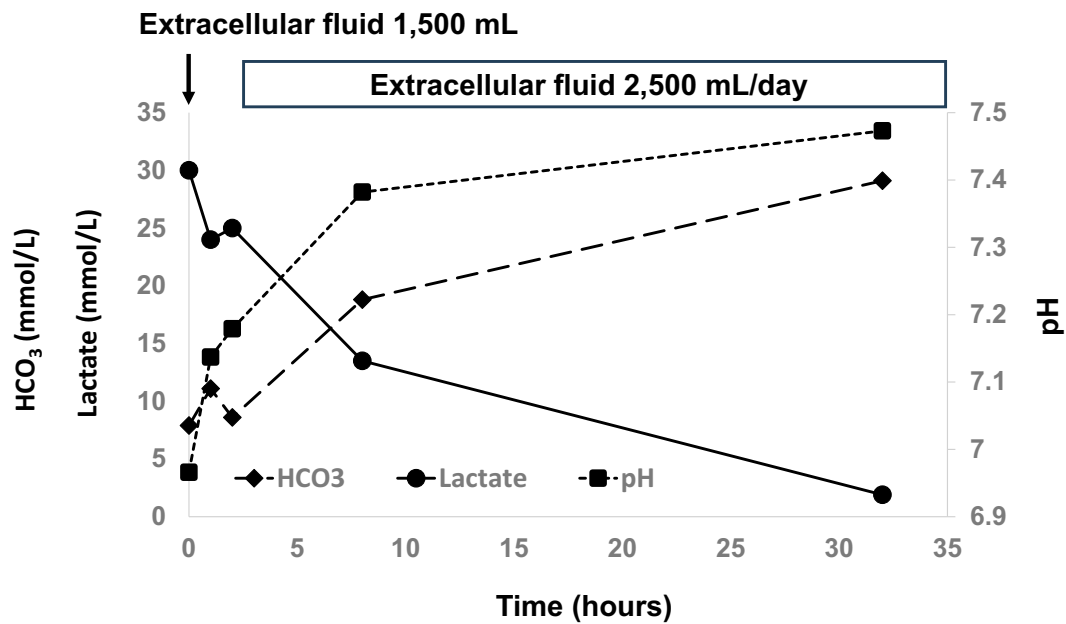
Figure.   Clinical Course.

Table 2.   Clinical Characteristics of Patients with Alcohol-induced MALA.

Age (years old)	65	55	69	44	35
Sex	Male	Male	Male	Female	Male
Dosage of metformin (mg/day)	1,000	750	None noted	5,000	1,000
Alcohol intake (g/day)	260	135	216	90	125-150
Last intake of alcohol	The day of admission	The day of admission	The day of admission	The day of admission	The day before admission
Serum creatinine concentration at baseline (mg/dL)	0.77	0.9	None noted	None noted	None noted
Serum creatinine concentration at admission (mg/dL)	1.4	2.7	1.4	0.94	None noted
Treatment	Infusion	Dialysis	Dialysis	Dialysis	Infusion
Outcome	Survived	Survived	Survived	Survived	Survived
Citation	Present case	[8]	[9]	[10]	[6]

MALA: metformin-associated lactic acidosis

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