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CASE REPORT

Anion gap-opening metabolic acidosis and urinary findings in the early diagnosis of ethylene glycol poisoning: A case report

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Abstract

Causative agent identification is important in the treatment of poisoning. We report the case of a patient who presented with an altered level of consciousness after drinking a fluorescent pink liquid. Upon measuring the anion gap and urinary calcium oxalate level, the patient was diagnosed with early ethylene glycol poisoning.

KEYWORDS

anion gap, ethylene glycol, pseudo-elevation of lactate levels

1 | INTRODUCTION

Japan has an increasing elderly population and a reportedly high incidence of accidental ingestion of cleaning and bleaching agents, partial dentures, and medication packaging misuse.[1]

Ethylene glycol (EG) is found in household products, such as refrigerants and antifreeze. EG poisoning is easy to determine when what was accidentally ingested or eaten is known, but it is difficult to diagnose when the consumed substance is unknown. Furthermore, the definitive diagnosis of EG poisoning involves the confirmation of EG presence in the plasma, but many medical institutions cannot rapidly measure its blood concentration.[2] Therefore, it is necessary to diagnose EG poisoning based on the patient's environment, general condition, and laboratory data.[3] Moreover, EG poisoning should be considered as a differential diagnosis in cases of anion gap-opening metabolic acidosis. Herein, we present a case of suspected EG poisoning due to fluorescent pink liquid ingestion, resulting in an altered level of consciousness and calcium oxalate crystals in the urine.

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2 | CASE REPORT

A 71-year-old Japanese woman was brought to the emergency department with an altered consciousness after drinking a "fluorescent pink liquid" (Figure 1). The patient had been living in serviced housing for older people for the past 2 years. However, the caregiver found her on a bed in the morning with a decreased level of consciousness with pink liquid spilled over her head. The patient was immediately transported to and managed in the intensive care unit (ICU) of a nearby secondary hospital. However, she was referred to our emergency department due to suspected poisoning 3 h after arrival at the secondary hospital. We received the patient after the previous hospital administered the following: a total of 2000 ml of extracellular infusion for hypotension (systolic blood pressure <60 mmHg), 20 ml of 50% glucose solution for a blood glucose level of 66 mg/dL, and 250 ml of 7% intravenous sodium bicarbonate for acidosis that resulted in a decreased level of consciousness. Furthermore, the past medical history included severe dementia and a significant decrease in activities of daily living, but no other significant medical history or intake of medications.

Moreover, a history of a suicide attempt by drinking liquid detergent occurred 1 month before. Hence, all disinfectants and detergents were removed. Furthermore, the patient was incapable of purchasing and possessing any of the above items 2 years ago when she entered the facility, considering the extent of her dementia.

Upon admission, the patient's Glasgow Coma Scale score was 9 (E3V2M4), and her pupillary light reflexes were bilaterally sluggish reactive. She had sinus tachycardia with a heart rate of 128 bpm (regular); other vital signs were normal with unremarkable physical findings. Blood examinations revealed an elevated white blood cell count and serum electrolytes, such as Na and Cl, while serum creatinine level was normal. Additionally, the arterial blood gas analysis showed severe metabolic acidosis, with a pH of 7.083, an HCO_3 level of 3.2 mmol/L, and an anion gap of 38.8 mmol/L. The theoretical value of plasma osmolality increased to 334.9 mOsm/kg-H_2O (Table 1). Chest radiograph showed no cardiac enlargement or pulmonary congestion. The results of a non-contrast computed tomography brain scan were normal.

FIGURE 1 Fluorescent pink liquid and unlabeled bottle. The liquid is not viscous and not reducing or oxidizing in nature

2.1 | Clinical Course:

The ambulance staff brought the pink fluid believed to have been ingested by the patient. Since she had a history of suicide, detergent, surfactant, pesticide, and corrosive poisoning was suspected. However, the fluid had no surfactant effect with low viscosity. The pH of the specimen collected from an unlabeled container was approximately 8, and specific gravity was found to be approximately 1.05. Nevertheless, redox reactions were also checked for copper (using a 10-yen coin made of copper), but no particular change was noted. These findings decreased the possibility of surfactant and corrosive poisoning.

Blood gas analysis performed in our hospital revealed anion gap-opening metabolic acidosis. The differential diagnoses are summarized in Table 2. We suspected methanol and EG poisoning since these liquids are available in Japan. The osmotic gap could not be confirmed because plasma osmolality was unavailable in our hospital. Calcium oxalate (Figure 2) and drug crystals (Figure 3) were found in the urine sediment, and a diagnosis of EG poisoning was made.

After collecting blood samples, sodium bicarbonate was administered intravenously to correct metabolic acidosis, and 10% ethanol (450 ml of 5% glucose solution +50 ml of anhydrous ethanol) was administered for 2 h to detoxify EG. Furthermore, fomepizole, an antagonist for EG and methanol, was procured from the nearby prefecture, and then the patient was admitted to the ICU. Moreover, hemodialysis was performed for 5 h on admission to improve acidosis and remove EG from the blood. After the initiation of hemodialysis, the blood pressure increased, and the patient regained consciousness after 2 h. No adverse events due to hemodialysis were observed. However, the lactate level remained high; therefore, the effect of toxic metabolism was considered, and fomepizole was administered until the 3rd day of hospitalization due to the high lactate level. Moreover, calcium oxalate and drug crystals were observed in urine until the 3rd day of admission, but the size and number of crystals decreased every day.

A component analysis performed later by the police department revealed that the main component of the pink liquid was EG, and the patient's blood EG concentration of

TABLE 1 Laboratory data from the time of arrival to the first day of hospitalization

	Reference range in adults	On arrival Previous hospital	On arrival Our hospital	After hemodialysis	On day 1 of hospitalization
Peripheral venous blood					
Red blood cell ($\times 10^6/\mu L$)	3.86–4.92	4.65	3.73	2.93	2.62
Hemoglobin (g/dL)	11.6–14.8	14	11.3	8.9	7.9
Hematocrit (%)	35.1–44.4	48.4	38.5	28.8	24.1
White blood cell ($\times 10^3/\mu L$)	3.3–8.6	7.73	18.3	13.6	8.3
Differential count (%)					
Neutrophils	42.4–75	67.2	89.4		78.9
Lymphocytes	32.4–47.7	26.5	5.4		14.8
Monocytes	5.4–9.0	4.5	4.7		6.0
Eosinophils	0.4–8.6	1.2	0.1		0.1
Platelet count ($\times 10^4/\mu L$)	15.4–34.8	39.2	33.9	22.3	18.4
Sodium (mmol/L)	138–145	150	160	147	136.1
Potassium (mmol/L)	3.6–4.8	5.7	4.9	2.9	4.1
Chloride (mmol/L)	101–108	112	114.8	110	102.0
Urea nitrogen (mg/dL)	8–20	16.3	18.5		7.1
Creatinine (mg/dL)	0.46–0.79	0.69	0.73		0.64
Glucose (mg/dL)	73–109		150		126
Alcohol (mg/dL)	<10		10↓		
Arterial blood gas					
pH	7.35–7.45	6.947	7.083	7.382	7.444
Partial pressure of carbon dioxide (mmHg)	32–48	10.5	11.3	26.0	35.7
Partial pressure of oxygen (mmHg)	83–108	148.1	141	133.0	138.0
Actual bicarbonate (mmol/L)	21.2–28.3	2.2	3.2	15.1	24.1
Lactate (mg/dL)	4.5–14.4	55.1	155	149	38

Note: Abbreviations: pH, power of hydrogen.

TABLE 2 Differential diagnosis for anion gap-opening metabolic acidosis (The Sanjay Saint, Craig Frances. Saint-Frances guide to inpatient medicine second edition p 288)

M-Methanol
U-Uremia
D-Diabatic ketoacidosis
P-Paraldehyde
L-Lactic acid
I-Isoniazid
E-Ethylene glycol
R-Rhabdomyolysis
S-Salicylic acid

398 mg/dL (the reference value of <20 mg/dL) measured upon admission confirmed the diagnosis. Additionally, the plasma osmotic pressure was 419 mOsm/kgH_2O, indicating an osmotic gap.

Due to the patient's old age and adjustment to the facilities, the recovery was slow. However, the patient was discharged without any sequelae on the 29th day of hospitalization. After a thorough investigation by the police, it was determined that there was no possibility of a crime and that it was an accident.

3 | DISCUSSION

EG poisoning is rare in Japan but common in the United States, with 6,739 cases reported to the American Association of Poison Control Centers in 2019.[4] Accidental ingestion of an antifreeze or refrigerant may cause EG poisoning, which initially damages the central nervous system and causes cardiopulmonary and renal dysfunction.[5] However, the onset and progression are often inconsistent and unpredictable with various clinical

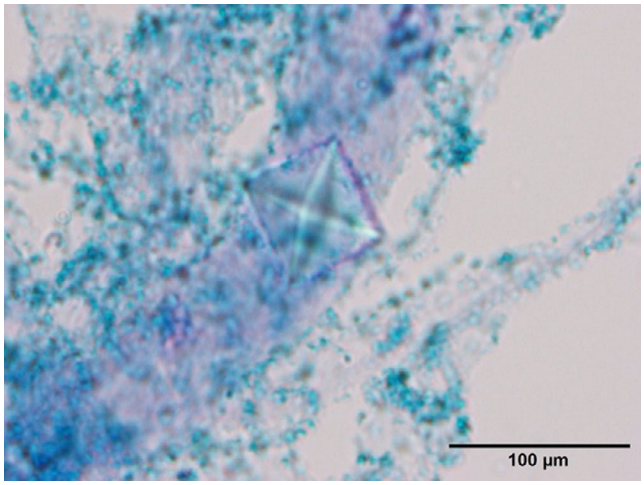

FIGURE 2 Calcium oxalate crystals in the urine. Crystal structures reminiscent of an octahedron-like structure were observed in urine until the third day

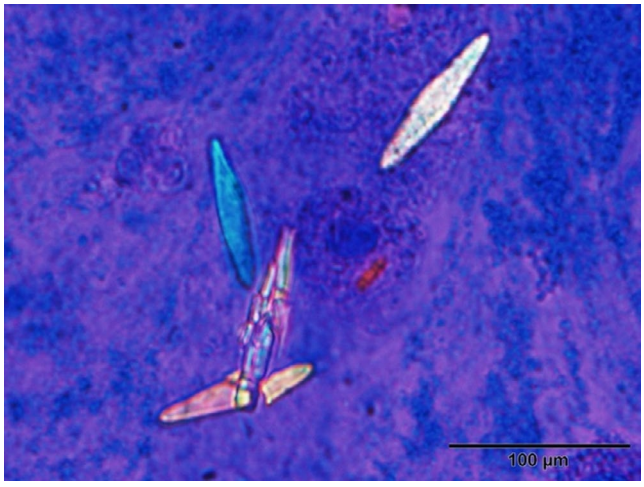

FIGURE 3 Drug crystals in the urine. Crystals with a change in color tone under polarized light were observed and were confirmed on the third day

presentations,[6] such as ST-segment elevation on electrocardiography[7] and pseudo-hyperlactatemia, based on the evaluation method.[8] EG is oxidized in the liver by alcohol dehydrogenase to glycolaldehyde, which is converted to oxalic acid, glyoxylic acid, and glycolic acid. The toxicity of EG is seen directly or indirectly through these metabolites, and even small amounts can be fatal. Furthermore, most of EG is absorbed in the gastrointestinal tract within an hour of ingestion, making an early diagnosis and therapeutic intervention critical.[9]

No hospital in Japan can directly analyze the composition or measure the blood concentration of EG. However, blood gas and urine sediment can be available diagnostic tools. The most important factor in the diagnosis was calcium oxalate and drug crystals in the urine, ruling out methanol poisoning. It has been reported that the drug crystals are polarized by observing under polarized light.[10] Figure 3 shows that the polarization and color tone vary with the angle of the crystals. Calcium oxalate crystals appear in the urine around 4–8 h after oral administration.[5] EG poisoning should not be ruled out even if calcium oxalate crystals are not present in the urine.

This case was initially managed with 10% ethanol since fomepizole was unavailable at the time. Ethanol has been used in EG poisoning as a competitive inhibitor of the enzyme, alcohol dehydrogenase. However, it is inferior to fomepizole because it requires monitoring. Moreover, ethanol has a sedative effect, and assessing the state of consciousness is difficult. Furthermore, renal impairment cannot be properly identified due to progressive dehydration. Since there is no direct comparison between the effects of ethanol and fomepizole and evidence to support their use, some studies suggest that the decision should be based on the availability and cost of the antidote, the hemodialysis facility, patient characteristics, and the physician's experience with the particular antidote.[11] However, oral ethanol has also been used because obtaining fomepizole and the off-label use of intravenous ethanol are difficult.[12,13] In the United States, fomepizole is used at a higher rate. In contrast, ethanol is used at a higher rate in other countries than in the United States[14] because fomepizole is difficult to obtain. When ethanol is administered intravenously for therapeutic purposes, the target blood concentration is often 100 mg/dL (22 mmol/L). However, the target blood concentration should be set based on the estimated concentration of EG, which is 1/4 of the EG concentration in the blood.[15] Since there are no facilities in Japan that can directly measure EG concentration in the blood, it should be estimated based on the amount ingested and a target blood concentration of 100 mg/dL.

The earlier the administration of the antidote, the better the outcome. Administration of antidote >6 h after arrival at the hospital has been associated with death and renal failure.[16] In this case, early diagnosis and recognition, and collaboration with the laboratory, pharmaceutical department, pharmaceutical company, and the police led to rapid intervention with fomepizole after the initial treatment with 10% ethanol infusion. The exact onset time was unknown, and it was unclear whether the treatment should be started within 6 hours; nonetheless, it was started immediately.

The lactate level was high in this case due to the chemical composition of lactate and glycolic acid, which led to a false-positive result.[17] Blood gas analysis was performed

using the current measurement method (ABL800 FLEX system). In EG poisoning or xylitol injection, glycolic acid rises in the blood and interferes with the electrodes, causing pseudo-high lactate levels. The elevated lactate level of the patient was not due to sepsis or the lack of oxygen in peripheral circulation because the blood pressure was stable, and there was no drop in the ScvO2 level, which indicates the patient's general condition and the continuation of fomepizole. However, it is important to differentiate between erroneous measurements and elevated lactate levels due to impaired oxygen utilization caused by sepsis or shock.

4 | CONCLUSION

We present the case of a patient with EG poisoning who was diagnosed early and treated with ethanol, fomepizole, and hemodialysis, resulting in recovery without any sequela. Blood gas and urine findings are essential for the early diagnosis of EG. Transvenous ethanol administration remains an important treatment option in areas where fomepizole is difficult to obtain.

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CONFLICT OF INTEREST
The authors declare that they have no competing interests.

AUTHOR CONTRIBUTION
Kentaro Ukita and Kanako Otomune involved in manuscript drafting, conception and design, and intellectual content. Ryo Fujimoto, Kanako Hasegawa, Koichi Izumikawa, Nobutoshi Morimoto, Kazuhiro Sasaki, and Akihito Hirasaki involved in revising and intellectual content. Koichi Takaguchi involved in supervision, revising, and intellectual content.

ETHICAL APPROVAL
Informed consent was obtained from the patient's family because the patient is incapable due to dementia.

CONSENT
The authors confirm that during submission the patient consent has been signed and collected in accordance with the journal's patient consent policy.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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