



# Clinical manifestations and renal pathology of ethylene glycol

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## Abstract

Ethylene glycol (EG) poisoning is a critical medical emergency often associated with suicide attempts in adults. EG is metabolized by alcohol dehydrogenase, leading to the formation of toxic metabolites that cause metabolic acidosis, renal failure, hypocalcemia, aciduria, and disorders of the central nervous and cardiovascular systems. Calcium oxalate, a metabolite of EG, contributes to acute tubular necrosis. Despite limited reports on human renal pathology, we present a case detailing renal pathology following EG ingestion. A 44-year-old male, admitted due to loss of consciousness, had ingested a lethal dose of EG. Blood tests indicated metabolic acidosis, while urinary examination revealed calcium oxalate crystals. Continuous renal replacement therapy corrected the acidosis; however, nephrogenic diabetes insipidus subsequently developed. A renal biopsy on day 31 revealed calcium oxalate crystal deposition and tubulointerstitial damage. Notably, various stages of crystal deposition, adherence, and degradation were observed. This case underscores the importance of considering EG poisoning in cases of unexplained metabolic acidosis and renal dysfunction, with renal biopsy serving as a valuable diagnostic tool. Understanding the renal effects of EG is essential for timely intervention and effective management of poisoning cases.

**Keywords** Ethylene glycol poisoning · Calcium oxalate crystals · Acute tubular necrosis · Nephrogenic diabetes insipidus

## Introduction

Ethylene glycol (EG) is a primary component of automotive antifreeze and is frequently involved in adult suicide attempts. In vivo, it is metabolized by alcohol dehydrogenase into toxic metabolites, leading to metabolic acidosis, renal failure, hypocalcemia, aciduria, and disorders of the central nervous and cardiovascular systems [1]. Renally, calcium oxalate, a metabolite of EG, contributes to acute tubular necrosis [2]. Despite limited reports on human renal pathology, this report details a case of renal pathology following EG ingestion. Examination revealed a substantial presence of calcium oxalate crystals within the renal tubular interstitium, along with observations of the tubular absorption and metabolism process.

## Case report

A 44-year-old man was admitted to the emergency room due to loss of consciousness. His wife found him unconscious at home around 4:00 am and immediately sought emergency medical assistance. The presence of a suicide note and an empty bottle of car antifreeze suggested a suicide attempt, with loss of consciousness likely due to ethylene glycol (EG) poisoning. The patient had a history of depression but no recent hospitalizations or regular medication use. He worked as a car salesman, and his family history was unremarkable. Upon admission, his height was 174.0 cm, weight 56.7 kg, and body mass index (BMI) 18.7 kg/m<sup>2</sup>. His level of consciousness was assessed as Glasgow Coma Scale (GCS) E3V4M5. Vital signs included a body temperature of 35.0 °C, blood pressure of 130/97 mmHg, heart rate of 95 beats/min, and respiratory rate of 25 breaths/min. Blood tests revealed a mildly elevated serum creatinine level of 1.16 mg/dL. Venous blood gas analysis showed a pH of 7.098, PCO<sub>2</sub> of 31.2 Torr, bicarbonate of 9.2 mEq/L, and an anion gap of 19.8 mmol/L, indicating a mixed acid–base imbalance with high anion gap metabolic acidosis and respiratory acidosis. Additionally, an osmolal gap of 24.7 mOsm/L was observed.

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Urinary examination showed 1 + proteinuria, 3 + occult blood, and 3 + calcium oxalate crystals (Table 1). Head imaging revealed no abnormalities contributing to impaired consciousness, while abdominal ultrasonography indicated bilateral renal enlargement.

Upon admission, the patient underwent continuous renal replacement therapy (CRRT) to remove ethylene glycol (EG) and its metabolites and to correct metabolic acidosis. Due to the severity of the EG intoxication, we considered administering fomepizole, an EG antagonist. However, the drug had to be ordered from a distant facility and was difficult to obtain at short notice. Therefore, we had to abandon the idea of administering it immediately. The acidosis resolved promptly after the initiation of CRRT and was corrected by the second day of hospitalization. On the fourth day of hospitalization, the peak serum creatinine level increased to 4.18 mg/dL, accompanied by polyuria exceeding 4 L per day. Subsequent hypertonic saline tolerance and DDAVP (1-desamino-8-D-arginine-vasopressin) tests confirmed

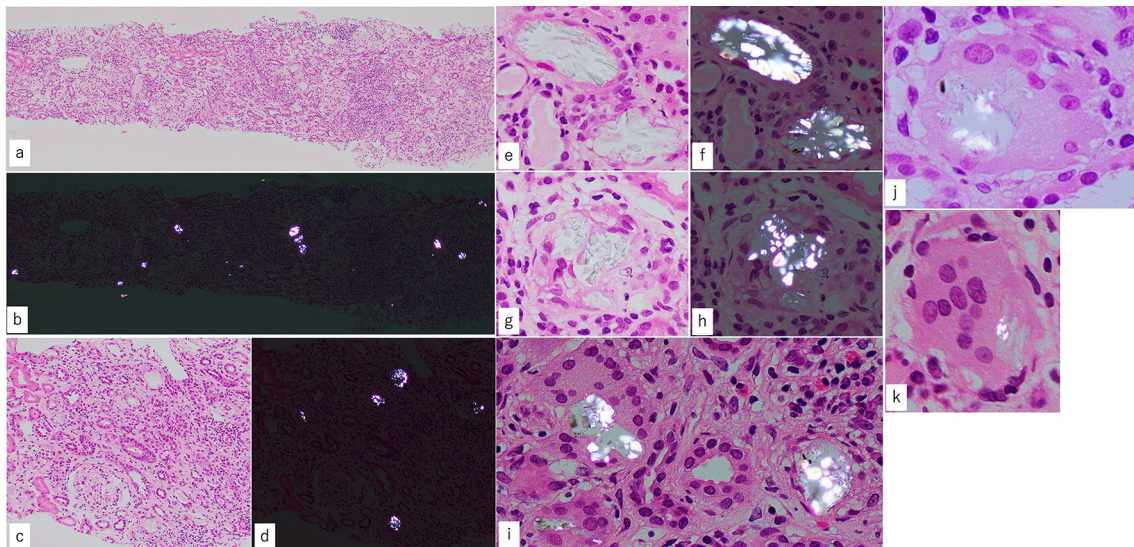
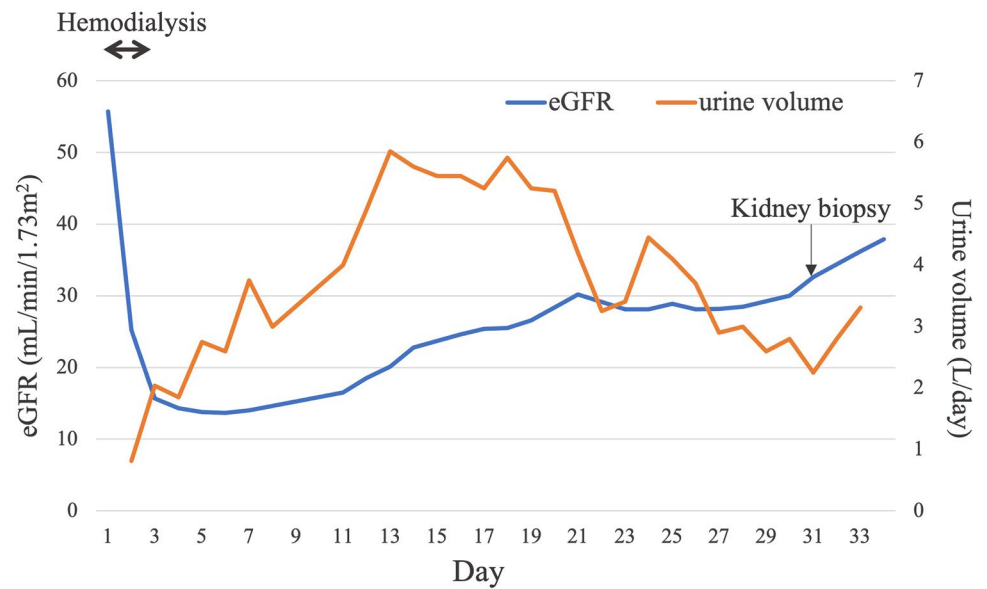
a diagnosis of nephrogenic diabetes insipidus. A renal biopsy was performed on the 31st day of hospitalization, when urinary output stabilized at 2.5 L/day and the serum creatinine level was 1.89 mg/dL (Fig. 1). Renal pathology revealed global sclerosis in 2 out of 42 glomeruli, with no proliferative or basement membrane changes in the remaining glomeruli. Tubulointerstitial lesions affected 50% of the cortex, characterized by inflammatory cell infiltrates, including eosinophils, foreign body giant cells, and granulomatous inflammation. Polarized light microscopy identified numerous calcium oxalate crystal deposits within the urinary tubular lumen and interstitium. Detailed observation revealed adherence of these crystals to the tubular epithelium, capture by overgrown tubular epithelium, and dissolution into granulomas after migration into the interstitium (Fig. 2). The patient was discharged on day 34 of hospitalization. In subsequent outpatient visits, the patient demonstrated improvement with a serum creatinine level of 1.04 mg/dL, and his urinary findings remained within normal limits.

**Table 1** Laboratory data on admission

Urine exam		Hematology		Biochemistry	
Specific gravity	1.007	WBC	$13.4 \times 10^3/\mu\text{L}$	TP	7.7 g/dL
pH	6.5	RBC	$6.19 \times 10^6/\mu\text{L}$	Alb	4.8 g/dL
Occult blood	(3+)	Hb	19.1 g/dL	UN	10 mg/dL
Protein	(1+)	Ht	60.30%	Cr	1.16 mg/dL
WBC	<1/HPF	MCV	97.4 fL	eGFR	55.7 mL/min/1.73m <sup>2</sup>
RBC	1-4/HPF	MCH	30.9 pg	T-Bil	0.5 mg/dL
Calcium oxalate	(3+)	MCHC	31.7 %	AST	16 IU/L
		Plt	$22.4 \times 10^4/\mu\text{L}$	ALT	16 IU/L
				LDH	196 IU/L
				ALP	66 IU/L
				$\gamma$ -GTP	27 IU/L
				CPK	99 IU/L
Blood gas analysis (venous blood)		Coagulation		TG	206 mg/dL
pH	7.098	PT-INR	1	HDL-C	57 mg/dL
PCO <sub>2</sub>	31.2 Torr	aPTT	23.1 Sec	LDL-C	101 mg/dL
PO <sub>2</sub>	28.5 Torr			Na	145 mEq/L
Bicarbonate	9.2 mEq/L			K	4.6 mEq/L
Base excess	- 21.3 mEq/L	Immunology		Cl	116 mEq/L
Lactate	3.1 mg/dL	CRP	0.04 mg/dL	P	3.6 mg/dL
Anion gap	19.8 mmol/L			Ca	9.8 mg/dL
				BS	102 mg/dL
				Posm	324 mOsm/L

WBC white blood cell, RBC red blood cell, HPF high-power field, Hb Hemoglobin, Ht Hematocrit, MCV mean corpuscular volume, MCH mean corpuscular hemoglobin, MCHC mean corpuscular hemoglobin concentration, Plt platelet, PT-INR prothrombin time-international normalized ratio, aPTT activated partial thromboplastin time, CRP C-reactive protein, TP total protein, Alb albumin, UN urea nitrogen, Cr creatinine, eGFR estimated glomerular filtration rate, T-bil total bilirubin, AST aspartate aminotransferase, ALT alanine transaminase, LDH lactate dehydrogenase, ALP alkaline phosphatase,  $\gamma$ -GTP  $\gamma$ -glutamyl transpeptidase, CPK creatine kinase, TG triglyceride, HDL-C high density lipoprotein cholesterol, LDL-C low density lipoprotein cholesterol, Na sodium, K potassium, Cl chlorine, P phosphorus, Ca calcium BS blood sugar, Posm plasma osmotic pressure

**Fig. 1** Clinical course and treatment of the patient. A blue line indicates estimated glomerular filtration rate (eGFR), and an orange line indicates urine volume



**Fig. 2** Images of oxalate crystals in the renal tubulointerstitium. **a** Under low magnification, calcium oxalate stones are difficult to identify with standard HE staining alone (HE,  $\times 20$ ). **b** However, using polarized light, the stones become visible (HE, under polarized light  $\times 20$ ). **c** Similarly, even with another low magnification HE staining, calcium oxalate stones are difficult to identify (HE,  $\times 40$ ) but **d** can be visualized with the use of polarized light (HE, under polarized light  $\times 40$ ). **e** Calcium oxalate crystals attached to regenerated cells of flattened tubules (HE,  $\times 400$ ). **f** These crystals

show birefringence under polarized light (HE, under polarized light  $\times 400$ ). **g** Calcium oxalate crystals present in the tubules and overgrown by the tubular epithelium (HE,  $\times 400$ ). **h** These crystals also show birefringence under polarized light (HE, under polarized light  $\times 400$ ). **i** Different forms of calcium oxalate crystals are present in the tubulointerstitium (HE, under polarized light  $\times 400$ ). **j** Calcium oxalate crystals taken up by granulomas (HE, under polarized light  $\times 800$ ). **k** Calcium oxalate crystals broken down by granulomas (HE, under polarized light  $\times 800$ )

## Discussion

Ethylene glycol (EG) poisoning has long been recognized worldwide [3], but the Japan Poison Information Center reported only seven cases in 2022, a small number for

Japan [4]. However, automotive antifreeze is inexpensive and relatively easy to obtain from car accessory stores and online in Japan. Therefore, the actual number of poisonings may be higher. The lethal dose of EG is documented as 1–1.5 mL/kg or 100 mL/70 kg body weight [5]. In this case, the patient, weighing 56.7 kg, ingested

at least 220 mL, surpassing the fatal dose. Approximately 80% of EG is metabolized in the liver (half-life 3–8 h) and 20% is excreted by the kidneys (half-life 18–20 h) [5]. Metabolism in the liver is mainly carried out by alcohol dehydrogenase, resulting in the formation of glycol aldehyde. Subsequent metabolism by aldehyde dehydrogenase produces glycolic acid, oxalic acid, and the final metabolite, calcium oxalate [5]. EG acts as an osmotic agent, and when it enters the bloodstream, it causes an osmotic gap. As it is metabolized, the metabolites cause metabolic acidosis. EG has a half-life of over 3 h, so the transition from an osmotic gap to raised anion gap metabolic acidosis is estimated to take more than 3 h. However, this period may be longer if large amounts are ingested or if the metabolism is slowed by the co-ingestion of ethanol [3]. In this case, the patient was unconscious upon transport, making the exact time of EG ingestion uncertain. The presence of raised anion gap metabolic acidosis together with an osmotic gap on admission and the presence of calcium oxalate crystals on urinalysis suggested that more than a few hours had passed since EG ingestion. The fact that the osmotic gap improved relatively quickly after admission, but the raised anion gap metabolic acidosis remained robust, suggests that the EG was being metabolized appropriately. Blood purification was performed to correct this persistent metabolic acidosis and to remove the metabolites of EG.

The renal effects of EG include proximal tubular damage induced by calcium oxalate and direct damage to the tubules by its metabolites glycolate, glycolaldehyde, and glyoxylate [8]. Renal pathology typically shows calcium oxalate deposition in the tubules and tubular necrosis with preserved glomerular structure [2]. Similarly, in this case, tubulointerstitial damage predominated with mild glomerular involvement. As the patient had no history of hypertension or diabetes mellitus that could lead to chronic renal failure, EG was considered the primary cause of renal damage. The process of tubulointerstitial injury induced by calcium oxalate involves several stages. Initially, calcium oxalate becomes supersaturated in the tubule lumen, forming microscopic crystal nuclei. These nuclei grow, leading to increased oxidative stress and crystal adhesion to the tubule epithelium. Crystals attached to the tubular epithelium are internalized by endocytosis and degraded by lysosomes, with some being released into the interstitium and finally degraded by granulomatous cells [11].

A study of renal pathology in rats reported a detailed time course of renal pathology after EG administration [12]. This study observed that by day 25 after EG administration, most calcium oxalate crystals were present in the tubulointerstitium, where some were degraded by granulomatous cells. In the present case, renal biopsy on day 31 of admission showed a variety of calcium oxalate crystals

in different stages, ranging from presence in the tubular lumen to uptake into the interstitium and granulomatous degradation. In contrast to the rat study, calcium oxalate excretion from the tubular interstitium was shown to be incomplete even on day 31. Kusmartsev et al. demonstrated the process of calcium oxalate crystal phagocytosis by human macrophages *in vitro* and the factors influencing the process [13]. They found that not all crystals formed in the tubular lumen are taken up uniformly by the interstitium and that some remain deposited in the tubular epithelium before being taken up. This process likely reduces the excessive inflammation caused by large amounts of calcium stones. Although observed *in vitro*, this phenomenon may also have contributed to the delayed calcium oxalate excretion in this patient.

Performing invasive renal biopsy on patients with ethylene glycol (EG) poisoning is challenging in terms of indication, as renal biopsy is not required to diagnose EG-induced renal injury. However, identifying a large number of calcium oxalate crystals in renal pathology can provide an opportunity to suspect EG poisoning. This case provided valuable insights into the complex mechanisms of renal damage and recovery, particularly the processes of phagocytosis and absorption of calcium oxalate crystals, which are crucial for understanding and managing ethylene glycol poisoning.

## Conclusion

We experienced a case of severe metabolic abnormalities after ingestion of a lethal dose of EG. This was a valuable case because it allowed us to observe the effects of EG on kidney tissue and the process of calcium oxalate removal by the kidneys.

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**Data availability** All data generated or analyzed during this study have been included in this article and its supplementary material. Further inquiries can be directed to the corresponding author.

## Declarations

**Conflict of interest** The authors declare no conflicts of interest.

**Ethical approval** This article does not contain any studies with human participants or animals performed by the authors.

**Informed consent** The patient provided informed consent for the publication of this case report.

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