

## CASE REPORT

# The importance of the histopathological examination in lethal acute intoxication with ethylene glycol. Case report

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## Abstract

Ethylene glycol is a toxic alcohol that is mainly introduced into an organism through the digestive pathway. Its priority toxic metabolites are glycolic acid and oxalic acid. We present the case of a young person, of the male persuasion, without any personal pathological history, found unconscious and presenting signs of violence. The patient is emergency hospitalized presenting coma, convulsive syndrome, severe metabolic acidosis and a positive result for alcoholism. Anamnestic data is extremely poor. The results of the clinical and paraclinical examinations suggest a possible poisoning with toxic alcohols. Despite the drug treatment and the hemodialysis, the evolution is unfavorable, resulting in death one week after admission. Through the forensic examination, the followings were found: cerebral and leptomeningeal edema, focal cerebral microhemorrhages, bronchopneumonia, septic spleen, shock kidney, hepatic fatty dystrophy, excoriated plaques in the head area. The histopathological (HP) examination confirms the macroscopic diagnosis and identifies the presence of calcium oxalate crystals in the kidney tubules. Subsequently, the toxicological examination of the biological samples taken from the corpse at the forensic examination, confirms the presence of the glycolic acid. Postmortem, the investigation conducted by the criminal investigation authorities confirms the oral ingestion of antifreeze. The absence of a positive history, along with alcohol consumption, nonspecific clinical symptomatology and the absence of calcium oxalate in urine are trap elements in the diagnosis of acute ethylene glycol poisoning. The presence of calcium oxalate in tissues, identified through the HP examination, is an extremely important factor when establishing the cause of death.

**Keywords:** ethylene glycol, death, calcium oxalate, nephrotoxicity, histopathological examination.

## Introduction

Ethylene glycol is a toxic alcohol that is mainly introduced into an organism through the digestive pathway, rarely dermal, respiratory or ocular. Chronic dermal and inhalation exposure are uncommon [1]. Its priority toxic metabolites are glycolic acid and oxalic acid. Ingestion is often accompanied or preceded by alcohol consumption. Ethylene glycol is a colorless, odorless and viscous dihydroxy liquid, it has a sweet taste and it is water, acetone and ethanol soluble [1, 2]. The lethal dose is 1–1.4 mL/kg body weight of pure ethylene glycol. It is fast absorbable in the digestive tract, the plasma peak occurring at about 1–4 hours after ingestion. Without treatment, a serum level above 20 mg/dL is associated with mortality in 98% of cases [3, 4]. Ethylene glycol is often used as a cooling liquid in radiators and in the synthesis industry (textile, cosmetics, varnishes, etc.). It can also be found in several commercially available chemicals: antifreeze, brake fluid, various solvents, stabilizer of sparkling agents, liquid for domestic radiators, plasticizer for glue [1, 2, 5].

From a legal point of view, ethylene glycol poisoning can be voluntary (suicide, homicide) and involuntary (accidental and occupational exposure) [2, 6]. A thorough

investigation, conducted by the law enforcement authorities corroborated with the results of the forensic necropsy, allows the establishment of the judicial probation of the death of a person following the administration of toxic substances. Ethylene glycol intoxication is often accidental (common in children) or suicidal (in teenagers, adults), homicide or occupational exposure by violating labor protection measures cases being rarely encountered [2]. The most common type of intoxication with ethylene glycol is acute form. The toxicity is influenced by several factors: toxin-dependent factors, body-dependents factors, factors dependent on the body–toxin interaction and environmental factors [7].

In cases of violent deaths, investigation of the causes and circumstances of occurrence is a must, the forensic medical examination having a determining role [6–9].

In forensic practice, when suspicions of intoxication exist, no matter the nature of the toxic, the on-site examination is extremely important. The on-site examination consists of both collecting investigation and anamnestic data, regarding the examined person, and identifying the supposed toxin and collecting evidence in the investigated area. Furthermore, according to the evidence, assessments regarding the position of the body/corpse and the possibility of survival and victim's movement, after the

ingestion of the toxin, are made [8]. In these cases, along the external and internal examination of the corpse, biological products will be sampled during the forensic autopsy. These samples will be analyzed in the toxicological examination, as well as the histological examination: blood, urine, stomach and stomach contents, tissue fragments [2].

### Aim

The purpose of this paper is to highlight the importance of the histopathological (HP) examination in acute lethal intoxication with ethylene glycol in forensic practice, when the forensic physician faces negative anamnestic data and incomplete provided investigation data.

## Case presentation

### Clinical status

We will present the case of a young, 36-year-old male, deceased, with no personal pathological history, laborer. Seven days ago, the victim was found unconscious by work colleagues, presenting excoriated face plaques and epicranial hematoma. Emergency ambulance services were telephonically requested. The patient was emergency hospitalized, presenting: coma [Glasgow Coma Scale (GCS) 5], tachycardia, oliguria, grand mall convulsive syndrome with hemodynamic instability, hypotension, severe metabolic acidosis (biochemically and hematologically), progressive nitrogen retention, elevated serum creatinine 5.59 mg/dL and serum urea 124.12 mg/dL, leukocytosis and neutrophilia. The urinalysis emphasized the presence of leukocyturia and a mild proteinuria. The urinary toxicological test result was negative. The blood alcohol content was 0.2 g‰. Emergency ventilation and mechanical ventilation support, as well as forced diuresis, cerebral depletion and hydroelectrolytic rebalancing were conducted.

The anamnestic data was extremely poor; the family denies the ethylene glycol ingestion and confirms the consumption of ethyl alcohol 18–22 hours prior. It was confirmed that the victim was intoxicated and suffered a cranial cerebral trauma (epicranial hematoma) and craniofacial trauma (excoriated face plaques in the right supra-orbital, zygomatic and nasal pyramid area) by falling. The victim's condition in the last 12 hours was unknown, he was alone at home during the night, and then went to work.

Upon admission, the computed tomography (CT) skull shows only a diffuse cerebral edema, while the abdominal echography reveals bilateral renal interstitial nephropathy. The results of the clinical (neurological, surgical, gastroenterological and nephrological consult) and paraclinical (CT skull, blood and urine laboratory tests) examinations determine the following: "Etiologically unspecified coma, possibly caused by poisoning with toxic alcohols. Acute kidney failure. Secondary craniofacial trauma". Regarding the patient's development, right after admission, he presents hemodynamic instability, anuria, repeated convulsions, altered consciousness (GCS 3), anion gap 31.7 mmol/L. An emergency hemodialysis session was established, without any neurological improvement.

During hospitalization, the hemodialysis and supportive treatment were followed by hemodynamic deterioration, which requires isotropic support. The general condition remains altered, the patient continues to present severe metabolic acidosis, hepatic impairment (increased transaminases), hypocalcemia, hematuria, proteinuria, with a disadvantageous prognosis and deterioration of the cerebral and renal function. Before long, a clinical picture of brain death (confirmed by the electroencephalogram), an acute renal insufficiency with acute toxic tubular necrosis and decompensated metabolic acidosis appear. Despite the drug treatment and hemodialysis, the evolution was unfavorable, resulting in death by septic complications after a 7-day hospitalization period.

### Forensic autopsy

A forensic autopsy was required to establish the causes of death. Through the autopsy of the corpse, the external and the internal examinations revealed several signs of violence: epicranial hematoma in the right parieto-occipital region, excoriated plaques at the base of the nasal pyramid, right zygomatic, supraorbital and fronto-temporal area and infiltrated blood in pericranial tissues in the right frontal, median and right parieto-occipital region. These violence lesions did not interfere with the tanatogenerator mechanism. The macroscopic anatomopathological diagnosis, established during the autopsy, was: pluriorganic stasis, cerebral and leptomeningeal edema, focal cerebral microhemorrhages, pleural effusion, bronchopneumonia, pulmonary edema, anthracosis, coronary arteriosclerosis, acute gastric ulcers (of stress), hepatic fatty dystrophy, septic spleen, shock kidney, excoriated plaques in the head area, infiltrated blood in soft pericranial tissues, traces of venous puncture/catheters (Figures 1–3).

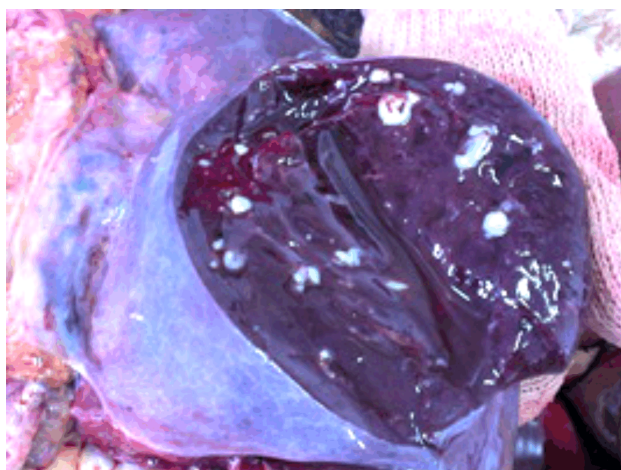
Several biological samples were collected from the corpse, during the necropsy, for complementary examinations: for the toxicological examination – blood and tissue fragments (liver, kidneys) and for the HP examination – fragments of tissues (lung, kidney, brain, heart, liver, spleen, stomach).

For the HP examination, all specimens obtained from autopsy were fixed in 10% formalin and embedded in paraffin. Sections of 4–6 µm were stained with Hematoxylin–Eosin (HE). Also, to capture the images, a Leica 300DM with high definition (HD) photo camera microscope was used.

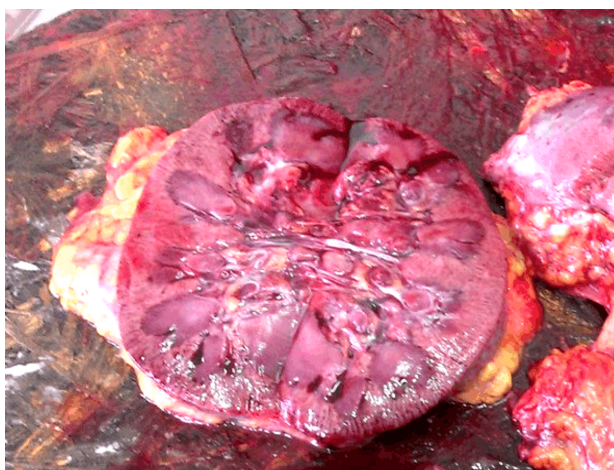
The HP examination reveals: lung – bronchopneumonia, pulmonary edema, stasis, anthracosis (Figure 1); kidney – periglomerular edema, renal stasis, hyaline cylinders, retained basal membranes, amorphous crystals (calcium oxalate crystals) – acute tubular necrosis (Figure 4); brain – pericellular and perivascular edema, cerebral stasis, cerebral focally ischemic areas, cerebral microhemorrhages (Figure 5); heart – coronaro-myocardiosclerosis; liver – vacuolar dystrophy and liver congestion; septic spleen; stomach – acute gastric ulcers (of stress).

The HP examination confirms the macroscopic diagnosis and identifies the presence of calcium oxalate crystals in kidney tubules. Calcium oxalate crystals, present in the renal tubules, lead to the diagnosis of acute intoxication with ethylene glycol.





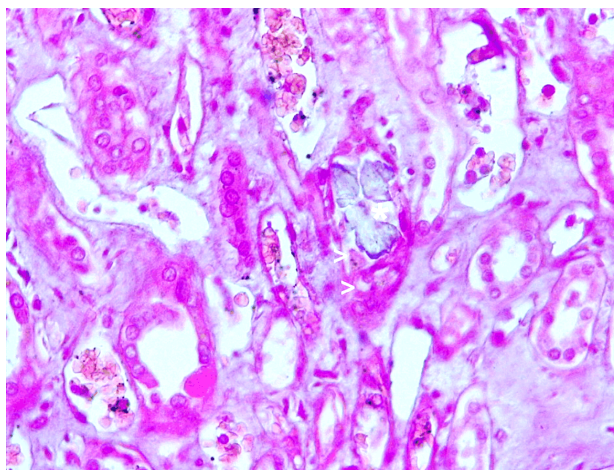
**Figure 1 – Macroscopic aspect of the lung: stasis, acute pulmonary edema and purulent exudate in the bronchial spaces, consistent with the diagnosis of bronchopneumonia.**



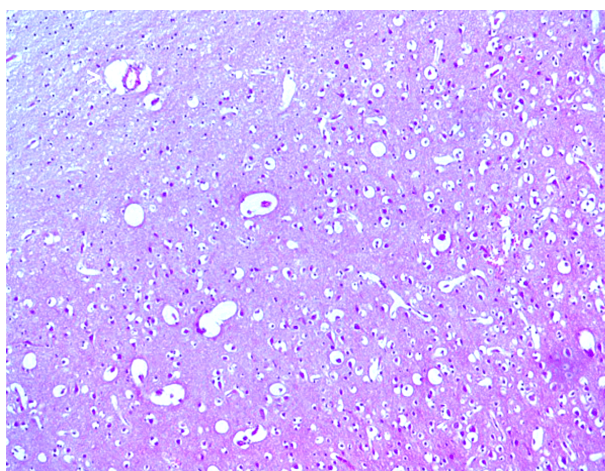
**Figure 2 – Macroscopic aspect of the kidney: shock changes.**



**Figure 3 – Macroscopic aspect of the brain: cerebral edema, narrow sulci, flat gyri.**



**Figure 4 – This section through the renal cortex shows, at a microscopic level, congested blood vessels and numerous tubules with signs of acute tubular necrosis: ballooning and hydropic changes (“>”) of proximal tubules and calcium oxalate crystals (“\*”) in tubular lumina. HE staining, ×200.**



**Figure 5 – Microscopic aspect of the brain: this section through the brain shows the formation of optically blank spaces around blood vessels (“>”) or around cells (“\*”), consistent with changes in acute cerebral edema. HE staining, ×100.**

The toxicological examination, performed through the gas chromatographic method of the blood and organ fragments collected from the corpse during the autopsy, had a positive result for glycolic acid (ethylene glycol metabolite) (0.44 g% glycolic acid). The quantitative amount of glycolic acid, determined in the toxicological examination, was influenced (downwards) by repeated hemodialysis sessions, provided for the patient during hospitalization. Thus, the toxicological examination reveals the presence of glycolic acid in blood and confirms the acute intoxication with ethylene glycol.

## Discussions

Ethylene glycol acts as an oxidative and it is metabolized to CO<sub>2</sub> and formic acid. CO<sub>2</sub> is eliminated from the body through the lungs, while the other intermediate metabolites (oxalic acid, glycolic acid) are disposed through the renal system [6]. Its metabolism takes place at the microsomal hepatic level, influenced by the action

of the alcohol dehydrogenase (ADH). Glycolic, glyoxylic and oxalic acids cause the appearance of severe acidosis [4]. The oxalic acid combines with the calcium ions, leading to the formation of calcium oxalate crystals. The accumulation of calcium oxalate crystals may be multi-organic, most often occurring in the renal tubules, resulting in renal insufficiency after about 24–72 hours after ingestion. This is due to the tubular epithelial necrosis with decreased glomerular filtration that appears after ingestion [2, 4, 5]. Neurological toxicity results in cerebral edema, with or without calcium oxalate crystals accumulation. The calcium oxalate can also accumulate in the myocardium, resulting in the appearance of toxic myocarditis. This can lead to death by cardiac failure phenomena and conduction disturbances [2, 4, 5]. Thus, multisystemic affection occurs, presenting acute respiratory failure requiring mechanical ventilation support, acute renal failure requiring hemodialysis and altered consciousness (GCS 3) [4, 10].

Simultaneous alcohol and ethylene glycol consumption increases the half-life of ethylene glycol, leading to abnormal laboratory test results and symptoms.

In acute poisoning with ethylene glycol, clinical symptomatology is nonspecific, many signs and symptoms being common to other intoxications, make it difficult to establish a diagnosis. The toxicological examination, using the gas chromatography, determines the presence of ethylene glycol or its metabolites in the victim's blood. This represents the key element for the certainty of the diagnosis [3, 11].

In cases of chronic intoxication or acute poisoning, with the ingestion of a low dose of ethylene glycol, the result of the renal biopsy can play a major role, when determining the positive diagnosis. This result highlights important elements, which can identify the cause of renal dysfunction, caused by the presence of calcium oxalate in kidney tubules [11, 12].

Specific treatment in acute intoxication with ethylene glycol consists of emergency administration of a specific antidote: ethylic alcohol (competitive ADH substrate) or fomepizole (ADH inhibitor), after a well-established therapeutic scheme [3, 4, 13, 14]. Gastric decontamination is necessary only in cases when the moment of the toxic ingestion is known [5]. The blood alcohol concentration on admission was 0.2 g‰. There were no available data regarding the consumption of other toxic substances. In the hospital where the patient was admitted, the toxicological examination through the gas chromatography could not be performed.

In the presented case, the anamnestic data is extremely poor. The patient is in a comatose state, while the family confirms only the ingestion of ethylic alcohol 18–22 hours prior, without knowing the amount or the exact time of consumption. The negative history, the patient's serious condition on admission, the nonspecific clinical symptomatology, the absence of calcium oxalate in urine, postponed the administration of a specific antidote. These elements can create a trap in the diagnosis of acute intoxication with ethylene glycol.

In cases of violent and suspect deaths, investigation of the causes and circumstances of occurrence is a must,

the forensic autopsy having a determining role to establish the causes of death [15, 16]. If death occurs because of the acute poisoning, within 24 hours, the necropsy examination will identify signs of asphyxia, general stasis, massive cerebral edema, hemorrhagic gastric mucosa (due to irritative gastric action) and renal failure. The cause of death consists of vascular collapse and acute cardio-respiratory insufficiency [2, 6]. If the patient survives longer than 24 hours, death may occur due to renal failure, uremic coma and/or septic complications, observed both macroscopically and histopathologically [17]. In cases of longer survival, the presence of calcium oxalate crystals in tissues (kidneys, brain), identified at the HP examination, confirms ethylene glycol poisoning [2, 6].

Corroborating the results of the necropsy with the results of the complementary examinations, we concluded: the victim's death was violent, caused by acute poisoning with ethylene glycol, evolving to a toxico-septic state. The head injuries (excoriated plaques, hematomas, blood infiltrates) could have been caused by hitting hard objects/surfaces, some presenting a rough surface, and may be 7–8 days old. These lesions did not have any role in the tanatogenerator mechanism.

The circumstances of death were established after compiling all the investigation data with the results of the forensic necropsy: the oral ingestion of antifreeze and alcoholic beverages was confirmed. In the absence of any eyewitnesses or supporting documents, it is difficult to determine whether the ingestion of ethylene glycol was accidental or voluntary, suicidal.

## ☞ Conclusions

Negative anamnesis, nonspecific clinical symptomatology, abnormal results of laboratory tests with the absence of calcium oxalate in urine, are elements that can create a trap for the diagnosis of acute intoxication with ethylene glycol. The amounts of ingested ethylene glycol, as well as the time between ingestion and treatment, are key elements for the prognosis and evolution of the disease. Immediate hemodialysis may correct the renal function, but the appearance of septic complications often results in the patient's death. The presence of calcium oxalate in tissues, identified through the HP examination, represents an extremely important element to establish the diagnosis of death in cases of acute poisoning with ethylene glycol.

## Conflict of interests

The authors declare that they have no conflict of interests. All authors read and approved the final manuscript.

## References

- [1] Caravati EM, Erdman AR, Christianson G, Manoguerra AS, Booze LL, Woolf AD, Olson KR, Chyka PA, Scharman EJ, Wax PM, Keyes DC, Troutman WG; American Association of Poison Control Centers. Ethylene glycol exposure: an evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol (Phila)*, 2005, 43(5):327–345.
- [2] Droc I, Droc S. Toxicologie medico-legală. În: Beliş V (red). *Tratat de medicină legală*. Vol. II, Ed. Medicală, București, 1995, 164–166.
- [3] Frasinariu OE, Rugina A, Jitareanu C, Russu R, Nistor N, Streanga V. Concomitant ingestion of ethylene glycol and

- ethanol: a diagnostic trap? Rom J Pediatr, 2015, 64(3):282–284.
- [4] Cox RD, Phillips WJ. Ethylene glycol toxicity. Mil Med, 2004, 169(8):660–663.
- [5] Nițescu VG, Ulmeanu AI, Ulmeanu CE. Toxic crystalluria – prevalence study in children poisoning. Rev Rom Pediatr, 2013, 62(1):83–91.
- [6] Dermengiu D. Patologie medico-legală. Ed. Viața Medicală Românească, București, 2002, 301, 316.
- [7] Iftenie V, Dermengiu D. Medicină legală. CH Beck, București, 2009, 279–281.
- [8] Salem A, Alexandrescu Gh. Cercetarea medico-legală la fața locului. În: Dermengiu D, Alexandrescu Gh (red). Medicina legală prosecturală. Ed. Viața Medicală Românească, București, 2011, 147–148.
- [9] Pusta CT, Dura H. Atherosclerosis – competing factor in the thanatogenesis of accidental violent deaths. Case report. Acta Med Transilv, 2013, 2(2):299–301.
- [10] Tanasescu A, Macovei RA, Tudosie MS. Outcome of patients in acute poisoning with ethylene glycol – factors which may have influence on evolution. J Med Life, 2014, 7(Spec No. 3):81–86.
- [11] Liberek T, Śliwarska J, Czurak K, Perkowska-Ptasińska A, Weber E, Rutkowski B. Prolonged renal failure in the course of atypical ethylene glycol intoxication. Acta Biochim Pol, 2013, 60(4):661–663.
- [12] Toth-Manikowski SM, Menn-Josephy H, Bhatia J. A case of chronic ethylene glycol intoxication presenting without classic metabolic derangements. Case Rep Nephrol, 2014, 2014:128145.
- [13] Brent J. Current management of ethylene glycol poisoning. Drugs, 2001, 61(7):979–988.
- [14] Kraut JA, Kurtz I. Toxic alcohol ingestions: clinical features, diagnosis, and management. Clin J Am Soc Nephrol, 2008, 3(1):208–225.
- [15] Pusta CT, Mihalache G, Buhas C, Pop O. A rare case of cardiac fibroma in a dead truck driver. Rom J Leg Med, 2015, 23(4):247–250.
- [16] Buhas C. Psychic family violence and pathological jealousy with tragic consequences: homicide. Aggress Violent Behav, 2013, 18(4):434–435.
- [17] Pusta C, Buhas C, Vilceanu N. Toxic-septic syndromes in violent death. Rom J Leg Med, 2006, 14(1):65–69.

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