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CASE REPORT

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Methamphetamine and carbon monoxide co-toxicity: an unusual case report and literature review

Uğur Ata[1*], Cemil Çelik[2] and Naile Esra Saka[3]

Abstract

Background Comprehending the toxic effects of substances co-detected in bodily fluids presents a formidable challenge. The combined toxic effect of carbon monoxide and methamphetamine remains a rarely discussed issue within the realm of scholarly literature. The main objective of this research is to delve into the potential intricacies of death mechanisms, unraveling the profound impact of both CO and methamphetamine on the heart.

Case presentation The cause and mechanism of death of a young man with toxic levels of CO–Hb and low-dose methamphetamine in his bloodstream were discussed in conjunction with the literature in this study. Methamphetamine levels of 30 ng/mL (0.03 mg/L) and 25.8% CO–Hb were detected in the blood of a 25-year-old individual who was found dead and without any disease.

Conclusions Although the amounts of methamphetamine and CO–Hb in the blood were not in the deadly range, it was determined that death occurred as a result of the combined action of these substances. In the present case, it was considered that death occurred as a result due to the combined cardiac effect of methamphetamine and CO, before the lethal blood CO level was reached.

Keywords Methamphetamine, Carbon monoxide, Case report, Mechanism of death, Cause of death

Background

After opioids, amphetamine-type stimulants take the second place in substance-related deaths. It has been reported that amphetamine-type stimulants are responsible for 7% of all substance-related deaths, a figure that has risen over time. Empirical findings have unveiled that the mortality risk among methamphetamine users stands elevated, ranging from 3 to 6 times greater when juxtaposed with their non-user counterparts. (Darke et al. 2017). Blood (plasma/serum) concentrations producing toxicity or clinically relevant adverse effects of drugs are considered toxic levels. Blood concentrations having caused coma and death of drugs are considered comatose-fatal (lethal) levels. Methamphetamine is often found along with other substances. These coexisting substances significantly compound the scenario, augmenting the inherent toxicity associated with methamphetamine. Methamphetamine's toxic range and comatose-fatal levels are highly variable. An increased risk of death has been reported with methamphetamine use, but the toxicity of methamphetamine and the level of lethal blood concentrations are not well recognized (Darke et al. 2017; Schulz et al. 2020; Cruickshank and Dyer 2009).

On the other hand; carbon monoxide (CO) emerges as a highly toxic gas formed because of the incomplete combustion of hydrocarbon (Liu et al. 2021; Al-Asmari

*Correspondence:
Uğur Ata
dr.ata52@hotmail.com
[1] Department of Forensic Medicine, Tekirdag Namık Kemal University, Tekirdağ, Turkey
[2] Kahramanmaraş Forensic Medicine Department, İstanbul Forensic Medicine Institute, Istanbul, Turkey
[3] Department of Forensic Medicine, Tekirdag Namık Kemal University, Tekirdag, Turkey

et al. 2021; Melez et al. 2017). CO binds tightly to the heme group in hemoglobin (Hb), impairing both oxygen delivery to tissues and ATP synthesis through binding to mitochondrial cytochrome C oxidase. Toxicity occurs due to the tight binding of CO to Hb, which replaces oxygen, and the inability to transport oxygen to the tissues (Liu et al. 2021; Al-Asmari et al. 2021; Chu et al. 2021; Kinoshita et al. 2020). CO–Hb levels above 50% are generally considered lethal in healthy individuals. On the other hand, levels below 18% of CO–Hb have no effect on healthy young individuals, but it is noted that CO–Hb levels exceeding 10% can be fatal in individuals with underlying heart disease (Palmeri and Gupta 2023).

Cases where methamphetamine causes death solely, and cases where it causes death in combination with other substances, make it difficult to determine toxic thresholds due to the overlapping of blood methamphetamine concentrations. However, it is stated that when in combination with other substances, methamphetamine can lead to death at lower concentrations (Al-Asmari 2021). There is a scarcity of literature addressing the combined effect of both CO and methamphetamine on the mechanism of death. In the existing studies, it has been observed that at the very least, one of the substances tends to attain lethal levels (Marc et al. 2021; Kumazawa et al. 2000). The cause and mechanism of death of a young man with toxic levels of CO–Hb and low-dose methamphetamine in his bloodstream were discussed in conjunction with the literature in this study.

Case presentation

The present research concentrates on the case of a 25-year-old male with no known medical history of any diseases. It was reported that the deceased started working at the restaurant three days ago; at the restaurant, he baked bread at 00:10; then, he moved to a room with two beds to rest; he was found dead in bed around 10:00 in the morning. During the crime scene investigation, an extinguished wood stove was found approximately 5–6 m away from the room where the deceased was located. Inside this stove, burnt aluminum foil and glass objects, assessed as drug paraphernalia, were found (Fig. 1). Among the bed pads was another glass object identified as drug paraphernalia ("meth pipe") (Fig. 1). The subject has previously used illegal narcotics, according to police documents.

At postmortem external examination, bright pink "living" coloration of the lividity was seen, and lividity was not fixed. Parallel old scar tissues associated with self-mutilation were seen on the anterior surface of the left forearm.

At the postmortem examination, the right and left lungs weighed 460 g and 435 g, respectively. Additionally, the heart weighed 355 g. Hyperemia and edema were evident in the brain, accompanied by mild edema in the lungs and petechial hemorrhages on the surface of the lungs, as well as occasionally petechial hemorrhages on the epicardial surface of the heart. In the lungs, there was moderate to severe anthracosis. The heart dissection revealed no macroscopic pathological change. Since no macroscopic pathological changes were observed in the heart, standard samples that needed to be taken at a minimum were obtained. These samples include: (1) four coronary artery samples (left main coronary artery, left descending coronary artery, left circumflex coronary artery, right coronary artery), (2) sinoatrial node area in the right atrium, (3) atrioventricular node area in the right atrium (Koch's triangle), conduction system sample involving the upper 1/3 of the tricuspid valve and septum, (4) right ventricular outflow tract myocardium (just below the pulmonary valve), (5) papillary muscles of the right ventricle, (6) papillary muscles of the left ventricle anterior and posterior, (7) myocardium of the apex region, (8) myocardium of the septum. Non-occlusive food particles were found in the trachea and main bronchi, which were attributed to the regurgitation of gastric contents. There were no macroscopic traumatic findings that could have resulted in death. All soft tissues and muscles, organs, and blood were revealed to be bright pink.

The histopathological examination yielded no discernible findings elucidating the cause of death. Histopathological examination of the heart revealed focal contraction band necrosis and congestion. However, no signs of myocardial infarction were found. The histopathological examination of the lungs unveiled alveolar space dilatation, the presence of foreign bodies and alveolar macrophages in some alveolar and bronchiolar lumens, congestion, and edema. The renal tissue was histopathologically examined and revealed congestion, sclerosis in some glomeruli, and tiny foci of erythrocyte extravasation (Fig. 2). Peripheral blood was placed in a tube containing Na–EDTA and sent for toxicological screening. The toxicological analysis of the blood yielded no traces of ethanol or methanol. Furthermore, the examination of lung tissue did not reveal the presence of any volatile substances. The blood analysis disclosed a concentration of 30 ng/ml methamphetamine (by GC–MS, liquid chromatography-mass spectrometry, and liquid chromatography time-of-flight mass spectrometry methods) and 25.8% CO–Hb (by CO oximeter). As there were no signs of decomposition in the case presented and the blood sample was sent for analysis without delay, it is reasonable to consider the determined CO–Hb level as indicative of the antemortem state. Amphetamine was not detected in the blood sample. However, in the qualitative toxicological analysis of the urine, methamphetamine, amphetamine, and 4-hydroxymethamphetamine were identified. Additionally, the presence of drug-active components, namely chlorpheniramine and pseudoephedrine/

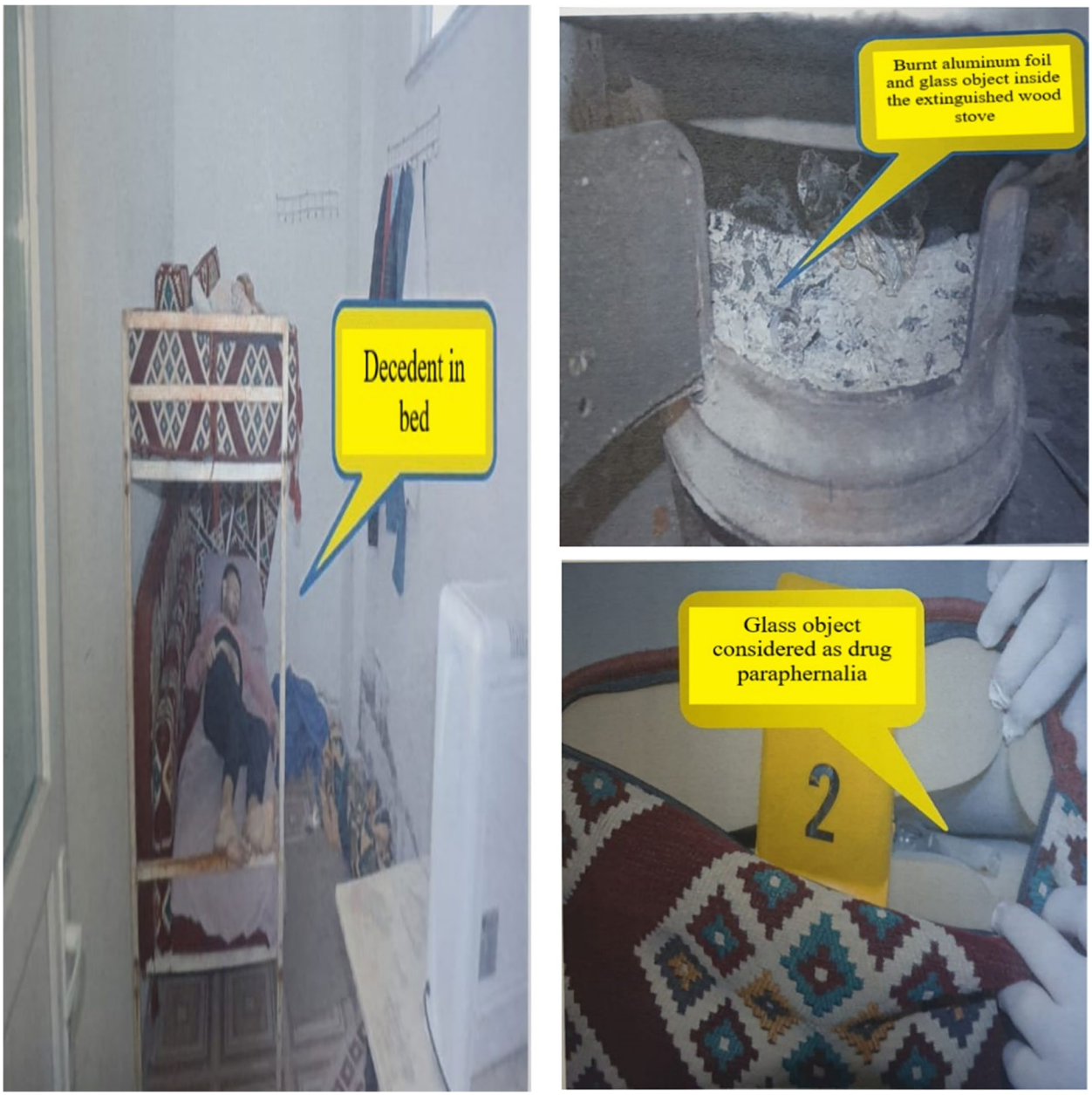

Fig. 1 Scene investigation findings

ephedrine, was established in the urine. Notably, the analysis of a glass object situated amidst the bed pads revealed the presence of methamphetamine via GC–MS analysis.

As a result, non-lethal levels of methamphetamine and carboxyhemoglobin were detected in the case; during the macroscopic examination in the autopsy, a bright pink appearance indicating carbon monoxide poisoning was observed in the tissues. Upon evaluating the toxicological analysis results, crime scene investigation findings, and autopsy findings together, it was concluded that the cause of death was attributed to the combined toxic effects of methamphetamine and CO. In this context, the categorization of the manner of death was established as accidental.

Discussion

Methamphetamine-related deaths

Methamphetamine is available in crystal, pill, and powder forms. While methamphetamine can be administered by inhalation, intranasal, intravenous, and oral routes,

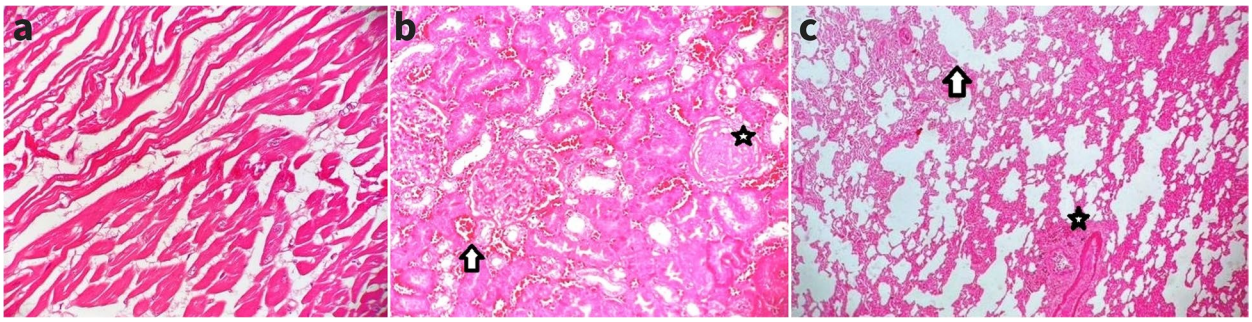

Fig. 2 **a** There is contraction band necrosis at myocardial fibers. The fibers lost cross striations and the nuclei were not clearly visible in most of the cells seen (hematoxylin and eosin × 200). **b** In histopathological examination, congestion (arrow) and glomerulosclerosis (star) were detected in the renal parenchyma (hematoxylin and eosin × 200) **c** There was edema in the lung parenchyma (arrow). Dilatation and alveolar macrophages were observed in the alveolar spaces (star) (Hematoxylin + Eosin × 100)

research indicates that inhalation is the most preferred way (Alniak et al. 2022; Al-Asmari 2021). Considering the presence of foreign bodies in the histopathological examination of our case's lung tissue and the paraphernalia (meth pipe) discovered at the scene, it was determined that the decedent received methamphetamine via inhalation, which is the most preferred route.

In low or moderate doses, methamphetamine has effects such as arousal, euphoria, mood elevation, frontal disinhibition, increase in cognitive functions, decrease in fatigue, increase in heart rate and blood pressure, and increase in body temperature. At higher doses, symptoms such as psychosis, irritability, and aggression occur (Cruickshank and Dyer 2009). Deaths attributed to methamphetamine are generally stated to occur due to pulmonary edema, pulmonary congestion, cerebrovascular hemorrhage (related to high blood pressure), ventricular fibrillation, acute heart failure, and hyperpyrexia. Despite relatively young ages, deaths are associated with cerebrovascular and cardiovascular complications (Cruickshank and Dyer 2009; Al-Asmari 2021).

In individuals with prolonged methamphetamine usage, notable manifestations encompass bruxism and dental fractures, stemming from heightened activation of the jaw muscles. Additionally, dental caries can arise as a consequence of oral dryness, a common occurrence in this context (Cruickshank and Dyer 2009; Lewis et al. 2021). Abusers may also suffer kidney damage due to rhabdomyolysis, and develop nephrosclerotic lesions (Lewis et al. 2021). In the deceased, nephrosclerotic lesions were noted, raising the possibility of a correlation with extended methamphetamine usage over time. Individuals who chronically use methamphetamine may exhibit histopathological changes in their myocardium, particularly fibrosis, with myocardial fiber hypertrophy being one of these changes (Akhgari 2017; Kaye et al. 2007; Schürer 2017). In the cardiac histopathology of the presented case, focal contraction band necrosis and congestion were detected, which could not be attributed to chronic use. In cases of drug overdose deaths, increases in lung weights due to pulmonary edema can be observed. Although mild edema was macroscopically observed in the lungs of the presented case, their weights are within normal limits.

Approximately fifty percent of methamphetamine is excreted in its unaltered form and the other half is 4-hydroxyamphetamine, amphetamine, and other compounds (Cruickshank and Dyer 2009). The presence of amphetamine in biological samples can emanate from two distinct origins. It might stem from direct ingestion of amphetamine or arise as a metabolite resulting from the ingestion of methamphetamine. Evaluating the proportion of amphetamine detected in the bloodstream becomes a valuable metric to differentiate between these scenarios, aiding in distinguishing whether it is attributable to direct substance consumption or as a consequence of methamphetamine metabolism (Al-Asmari 2021). Methamphetamine's presence can persist in the bloodstream for as long as 48 h after ingestion. It has been reported that it can be detected in urine for a duration spanning up to 7 days after a single oral dose of 10 mg. Through inhalation, an extensively favored mode of administration, methamphetamine is rapidly detected in the bloodstream, while it reaches its plasma peak value approximately 2.5 h following inhalation. This phenomenon is attributed to the decelerated absorption of methamphetamine retained within the airways (Cruickshank and Dyer 2009). In the presented case, 30 ng/ml of methamphetamine was detected in the blood. Amphetamine was not detected in blood but methamphetamine, amphetamine, and 4-hydroxymethamphetamine were detected in urine. The absence of methamphetamine metabolites (amphetamine, 4-hydroxymethamphetamine) in the blood and the low

levels of methamphetamine in the blood suggest that the individual's demise occurred shortly after inhalation of methamphetamine.

In the study by Schulz et al., it was stated that the toxic dose of methamphetamine lay within the spectrum of 0.2–1 mg/L and the lethal threshold encompassed ranges of 1–18 and 40 mg/L according to the presented case reports (Schulz et al. 2020). Studies have documented fatalities at a minimal blood methamphetamine concentration of 0.05 mg/L, juxtaposed with instances of survival at considerably elevated concentrations, such as 9.46 mg/L (Logan et al. 1998; Cruickshank and Dyer 2009). Although there are many factors such as polydrug use affecting toxicity and fatality, in general, 0.2–5 mg/L blood methamphetamine concentration is considered toxic, and blood methamphetamine concentration higher than 10 mg/L is lethal (Cruickshank and Dyer 2009). Al-Asmari's research discloses that the lowest blood methamphetamine concentration detected in deaths that were considered to develop due to solely methamphetamine intoxication was 116 ng/ml. In the same study, it was reported that the lowest blood methamphetamine plasma concentration in methamphetamine-related deaths (not solely methamphetamine; there are other contributing factors such as co-morbidity, and polydrug intoxication) was 55 ng/ml (Al-Asmari 2021). Could 30 ng/ml methamphetamine, which was detected in the present case, have caused death by synergistic toxic effect together with CO?

Carbonmonoxide-related deaths

In the study conducted by Liu et al., it was reported that ≥ 30% higher CO–Hb levels in CO poisoning-related deaths were observed in younger individuals (≤ 30 years), while CO–Hb levels of 10–30% were observed in individuals from all age groups (Liu et al. 2021). The lethal dose of CO may exhibit variability contingent upon factors of age, gender, the presence of additional disease, and individual tolerance (Al-Asmari et al. 2021). It is established that CO–Hb levels of up to 5% are regarded as within the normal range for non-smokers, while heavier smokers may exhibit levels of 10–13% that are still considered normal (Chu et al. 2021; Kinoshita et al. 2020). One of the prevailing hypotheses proposes that death may occur at lower CO–Hb levels in the presence of cardiopulmonary disease. In cases of alcohol and drug use, it would be accurate to assert that lower CO–Hb levels may lead to death due to their synergistic effect on the cardiopulmonary system. It has been reported that the following three criteria must be met to be called dead due to acute CO poisoning; the presence of CO source, the elevation of CO–Hb levels, and the presence of indicators of CO poisoning, exemplified by bright pink lividity (Liu et al. 2021). In the presented case, the following criteria for CO poisoning were fulfilled: An extinguished coal stove as a source of CO, a CO–Hb level of 25.8%, and bright pink lividity as a sign of CO–Hb poisoning. What we are really discussing is whether methamphetamine was a contributing factor in the death of this young man with CO poisoning. In this case, methamphetamine might have lowered the lethal CO blood levels to a lower threshold.

Mechanism of death, cause of death

Many studies have shown that methamphetamine use has acute and chronic harmful effects on the cardiovascular system (Karch et al. 1999; Cruickshank and Dyer 2009; Al-Asmari 2021). Methamphetamine exerts profound impacts on the cardiovascular system, giving rise to increased blood pressure, atherosclerosis, vasospasm, and the remodeling of cardiac tissue that can lead to arrhythmias and heart failure. There is evidence that methamphetamine is associated with the prolongation of QT intervals, consequently increasing the risk of initiating ventricular arrhythmias (Cruickshank and Dyer 2009; Al-Asmari 2021; Darke et al. 2017; Kevil et al. 2019; Nagasawa et al. 2018; Kaye et al. 2007). Potassium channel dysfunction in cardiac muscle cells is in question in acquired prolonged QT syndrome due to drug use. This dysfunction can lead to fatal arrhythmias in the presence of a predisposing factor such as hypokalemia or bradyarrhythmia (Nagasawa et al. 2018). It is stated that even very low doses of methamphetamine can trigger cardiac arrhythmia and this situation will be easier in the presence of additional factors. The use of multiple stimulant substances further increases the cardiac burden. If central nervous system depressants such as alcohol or opioids are taken together, it will be difficult to meet the increased need for cardiac oxygen demand associated with methamphetamine because they depress respiration, and the occasion for cardiac arrhythmia will be ready again (Darke et al. 2017; Kaye et al. 2007).

Additionally, CO has toxic effects on the heart with multiple mechanisms. CO may reduce the amount of oxygen delivered to the myocardium, complicating preexisting cardiac diseases. It inhibits ATP synthesis with cytochrome C oxidase blockade because of its direct effect on myocardial tissue, leading to anaerobic respiration, lactic acidosis, and apoptosis in myocytes. Elevated oxidative stress is accountable for inducing apoptosis within endothelial cells, which subsequently engenders coronary vasoconstriction. This sequence of events collectively leads to a reduction in myocardial perfusion (Chu et al. 2021). In our case, the fulfillment of the increased cardiac oxygen demand due to methamphetamine use was difficult due to the presence of CO–Hb,

and as a result, CO–Hb may have appeared as an additional factor triggering cardiac arrhythmia.

Another toxic effect of methamphetamine on heart tissue is elucidated by its activation of L-type calcium channels. By stimulating the L-type calcium channel of methamphetamine, calcium is released from the sarcoplasmic reticulum, consequently leading to the increased contraction of cardiomyocytes and increased cardiotoxicity (Lewis et al. 2021). Moreover, CO predisposes to the development of arrhythmia by increasing the sensitivity of myocytes to calcium (Chu et al. 2021). Considering these two effects in our case, methamphetamine may have increased the release of calcium in cardiomyocytes through the L-type calcium channel, and increased CO may have increased the sensitivity of cardiomyocytes to this increased calcium, in turn resulting in arrhythmia causing death.

Pathological contraction bands in the heart are an important histological hallmark of adrenergic stress caused by various mechanisms, intrinsic or extrinsic to the heart. Pathological contraction bands in the heart (focal contraction band necrosis detected in the presented case) may represent a sign of adrenergic stress linked with malignant arrhythmia/ventricular fibrillation (Baroldi et al. 2001). Fineschi et al. assert that acute lethal CO intoxication manifests as bradycardia, culminating in cardiac arrest marked by asystole, all transpiring without discernible signs of concomitant myocardial injury. A negative finding was seen in CO intoxication, whether accidental or suicidal, suggesting an anti-adrenergic effect of lethal anoxia despite a longer survival period. Formation of contraction bands, accompanied by the absence of interstitial hemorrhage, occurs exclusively upon the restoration of reoxygenation (Baroldi et al. 2001; Fineschi et al. 2000). The presence of contraction band necrosis in reoxygenation after CO intoxication is probably related to agonal or pre-terminal sympathetic stimuli to improve contraction. However, in many conditions, the frequency and extent of contraction band necrosis indicate an adrenergic role (Baroldi et al. 2001). As in our case, myocardial contraction band necrosis is common in postmortem histopathological examination in people using methamphetamine and similar stimulants (Karch et al. 1999). The contraction band necrosis observed in the presented case could have been caused by an adrenergic influence during the agonal period or/and an arrhythmia. The presence of non-obstructive gastric contents in the lungs draws attention to the adrenergic effect during the perimortem period in this case.

Pasarro et al. report that the mortality risk of HIV infection and cigarette smoking dramatically increases in methamphetamine-dependent gay-bisexual men (Passasro et al. 2019). According to the conducted studies, the increased risk associated with smoking is understood to be related to the adrenergic response to nicotine (Fineschi et al. 2000; Hanna 2006). In this context, considering that CO–Hb levels in heavy smokers are up to 10%, it may not be wrong to say that these individuals are at risk of developing arrhythmia from methamphetamine use. This presumed risk may be due to both the toxic effect of CO and the promoter of the adrenergic response to nicotine.

Considering all these mechanisms, It is highly probable that the cause of death was arrhythmia due to the combined effect of CO and methamphetamine. In light of the studies previously conducted in the literature, we can interpret the combined toxic effect as arising from synergistic effects on calcium metabolism in myocardial cells of these substances. Despite comprehensively evaluating the results, including those from the toxicological examination, establishing distinct anatomical evidence of cardiac arrhythmia proves to be challenging. Nonetheless, the abrupt death within the context of this case is posited to originate from a fatal cardiac arrhythmia. Based on the current data, another possible cause of death cannot be anticipated. However, the limitations of our study include the unknown duration of the deceased's exposure to CO, and whether the deceased had underlying cardiac disease.

Conclusions

While the literature does provide documented instances of toxic and lethal thresholds for methamphetamine, it is crucial to acknowledge that lethal dosages of methamphetamine can exhibit variation based on individual factors and contextual circumstances, mirroring the inherent variability observed with any given substance. In the presented case, it was considered that the death resulted from cardiac repercussions arising from the synergistic impact of methamphetamine and CO, without necessitating attainment of a lethal blood CO level. This case highlights the potential of methamphetamine to exert a contributory role in mortality, even at notably modest dosages. However, to demonstrate this, controlled animal experiments should be conducted to show the impact of CO and methamphetamine on each other's lethal levels. As a result, determining whether the plasma concentration of a substance is within therapeutic, toxic, or lethal ranges presents a complex challenge. Compounding this challenge is the potential disparity between postmortem samples and antemortem levels, further complicating the interpretation of analysis outcomes. Addressing these intricacies requires a comprehensive approach, wherein toxicology results are harmoniously evaluated alongside scene observations, medical history, and autopsy findings. On the other hand, this case reminds us that methamphetamine poses a significant risk to society even in very small doses, as it can be life-threatening.

Abbreviations

CO	Carbon monoxide
Hb	Hemoglobin
CO–Hb	Carboxyhemoglobin
GC-MS	Gas chromatography–mass spectrometry

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Author' contributions
CÇ performed the autopsy of this case. CÇ, UA, and NES interpreted the patient toxicology analysis result. UA and CÇ reviewed the literature. UA and CÇ wrote the manuscript with the support and suggestion of NES. All authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate
Permission was obtained from The Council of Forensic Medicine with the date 05.12.2022 and number 21589509/2022/1079 and the Helsinki Declaration rules were followed to conduct this study and the original article is attached with the approval form.

Consent for publication
Oral consent was received from the deceased's uncle after informing him of the purpose of the case report. No identifying private details are described within the case report. Consequently, we did not need to receive written consent.

Competing interests
The authors declare that they have no competing interests.

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