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CASE REPORT

TOXICOLOGY; PATHOLOGY/BIOLOGY

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Acute Arsenic Poisoning: Clinical, Toxicological, Histopathological, and Forensic Features

ABSTRACT: This report describes a suicide case by acute arsenic intoxication via intravenous injection. A 30-year-old woman injected arsenic As (V) (sodium arseniate disodique: Disodium Hydrogena Arsenik RP) in a successful suicide attempt. Three hours following administration, the woman developed severe digestive symptoms. She was admitted to a hospital and transferred to the intensive care unit within 12 h of the massive administration of arsenic. Despite therapeutic efforts, over the next 2 h she developed multiorgan failure and died. A postmortem examination was performed. Pulmonary edema and congestion of liver were apparent. As (V) and As (III) were determined by high performance liquid chromatography and inductively coupled plasma mass spectrometry after mineralization of samples by concentrated nitric acid. Toxicological analysis revealed high concentrations of arsenic in biological fluids as well as in organs. Histopathological examination showed a typical indication of myocarditis. These findings were in agreement with acute arsenic poisoning. The symptoms developed by this young woman (intoxication by intravenous administration) were comparable to oral intoxication. The clinical signs, survival time, and administration type are discussed in light of the literature on acute and chronic arsenic poisoning.

KEYWORDS: forensic science, arsenic, injection, intoxication, inductively coupled plasma mass spectrometry, autopsy, toxicology

Arsenic is the 20th most abundant element in the earth's crust and is present in all living organisms. It is found in natural sources, such as soil, water, air and food, and also in many manufactured products including insecticides, fungicides, herbicides, ceramic enamels, and preservatives for hides and is used in the manufacture of glass and fireworks (1). It is used in industry and in the therapeutic field, including dermatology and hematology. The clinical manifestations of acute arsenic toxicity after massive administration are diverse and have been described, in particular, with regard to the digestive, cardiovascular, neurologic, cutaneous, and renal systems (2). Although today acute arsenic poisoning is uncommon, here we report the first case of suicidal death by massive acute arsenic poisoning by intravenous injection.

Case Report

A young woman of 30 years of age was, according to her previous medical history, an alcohol abuser and consumed cocaine and heroin by intravenous injection. She began her alcohol and drug abuses at age 20 but stopped heroin and cocaine abuse 4 years prior to her death. She left the family home when she was 20 and was homeless for 6 years. Throughout this period, she drank heavily, especially on weekends. She eventually returned to the family home, but her relationship with her family was highly conflicted and argumentative.

In April 2007, on a Saturday night, her parents returned home from an outing and found their daughter prostrate on a sofa, experiencing abdominal pain and severe vomiting. A quarrel ensued and she went to her bedroom. Her family did not find this situation unusual, compatible with her alcohol intoxication, which was a usual occurrence. She mentioned no unusual circumstances, complaining only of abdominal pain. On Sunday morning, her abdominal symptoms worsened and her father decided to call a general practitioner. When the physician examined the young woman, she confessed to him that she had injected arsenic the previous evening. The physician called the emergency service, and the young lady was immediately transferred to a hospital. After admission, the woman's clinical state worsened further, and she was transferred to the intensive care unit. Blood samples were taken. About 14 h after the injection of the arsenic-containing substance, sudden circulatory arrest and death occurred, despite attempts at resuscitation. Under these particular circumstances, a crime scene investigation was undertaken by police, and an autopsy was performed.

Autopsy Findings

External examination revealed no traumatic injuries, although signs of injections in the left jugular area and wrist were found, which were consistent with resuscitation efforts.

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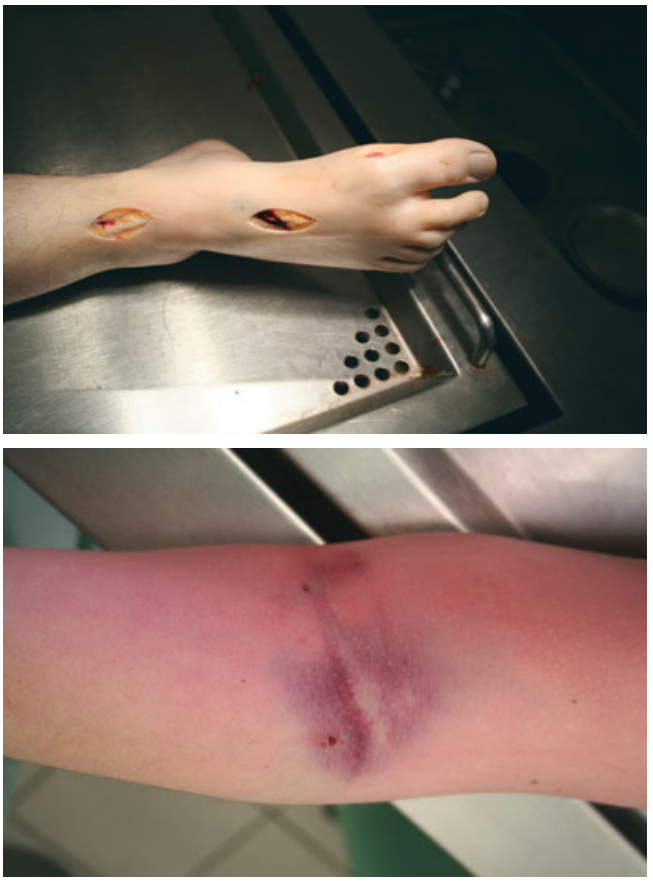

FIG. 1—*Marks of injections in the right foot and in radial and cubital veins. These injections were not performed by the hospital (intensive care unit). These findings are in agreement with the confession of the young woman.*

Injection marks were noted in the radial and cubital veins of the elbow and in the right foot; these specimens (injection sites: Fig. 1) were taken for toxicological analysis as they were not administered by the intensive care unit of the hospital. These indications were consistent with the young woman's confession to the physician that she was a drug abuser and she had injected arsenic.

During the autopsy, organ examination was normal and no organic macroscopic traumatic lesions were found. The heart, kidneys, and brain were congested. A significant hemorrhagic edema was found in the lungs. The heart weighed 310 g, and the wall of the left ventricle was slightly hypertrophic. The right lung weighed 1085 g and the left lung 1070 g. No vesicle formation was observed in the intestine.

Histopathological Aspects

The sites of injection in the skin revealed hemorrhagic lesions of the derma and hypoderma. The pathologist estimated that the injections were consistent with having occurred <24 h prior to death, and more precisely between 12 and 24 h. The main histopathological lesions were in the myocardium. The myocardium contained necrotic areas and myocarditis. Cellular necrosis of the myocardium and inflammatory infiltration of interstitial tissue were also found. Significant inflammation with the presence of numerous leukocytes and lymphocytes was noted. A perivasculitis with neutrophils in the myocardium was noted (Fig. 2*a,b,c*). The lungs had diffuse edematous alveolitis, and the kidneys and the liver were highly congested. These histopathological findings were consistent with arsenic poisoning. The intestines were normal.

Toxicological Findings

Methods

During her brief hospitalization, only peripheral blood was analyzed for toxicological studies. Postmortem fluid samples (blood samples, bile, gastric content, and urine) and hair as well as sections of internal organs (liver, kidney, lung, and venous injection sites in right foot, cubital, and radial vein areas) were examined for the presence of arsenic, and the results are reported in Tables 1 and 2.

Arsenic Determination——The toxicity of arsenic depends on its chemical form; therefore, determination of total arsenic concentration is not sufficient in clinical chemistry and in forensic cases. Total arsenic determination can be used as a screening test to rule out intoxication. Arsenic speciation can be carried out using several techniques. High performance liquid chromatography coupled with inductively coupled plasma mass spectrometry (HPLC-ICP-MS) is one of the most commonly used methods. The advantages of this hyphenated technique include chromatographic separation followed by the selectivity, sensitivity, and dynamic range of ICP-MS. Therefore, analysis and characterization of trivalent arsenic (As [III] or arsenite), pentavalent arsenic (As [V] or arsenate), and the metabolites monomethylarsonate (MMA) and dimethylarsinate (DMA) were possible. Arsenic speciation was determined by HPLC (Waters 515, Column: Agilent speciation G3288-80000, Precolumn: Agilent G3154-65002; Waters, Saint-Quentin en Yvelines, France; Agilent, Massy-Palaiseau, France) and inductively coupled plasma mass spectrometry (Agilent 7500 series) after mineralization of samples (2× 10 g of homogenized tissue, 2× 2 mL of blood or 2× 10 mL of urine) by concentrated nitric acid (1 mL/100 mg) and heat (1 h at 70°C). The mobile phase was prepared by adding

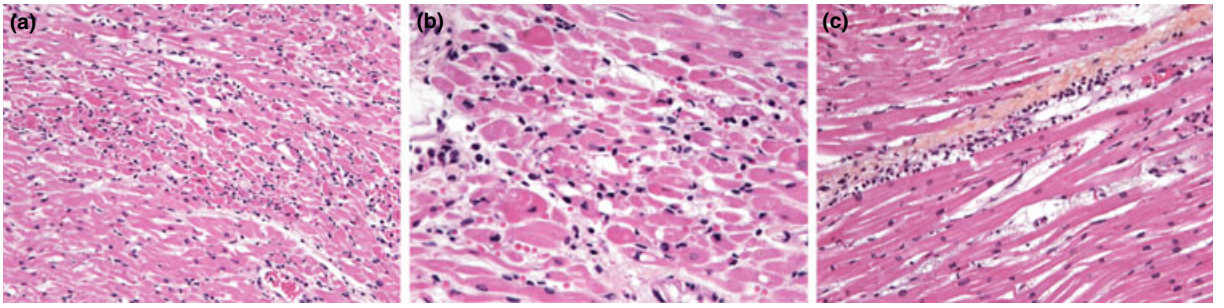

FIG. 2—*(a) Necrotic areas and myocarditis aspect. (b) Cellular necrosis of myocardium with inflammatory infiltration of interstitial tissue. (c) Inflammation with presence of numerous leukocytes and lymphocytes. Perivasculitis with neutrophils consistent with myocarditis (arsenic poisoning).*

TABLE 1—*Toxicological analysis of body fluid samples.*

Fluids	Antemortem	Postmortem	Literature (21,22)
Femoral blood	600: As (III) 39: As (V)	–	
Cardiac blood	–	ND: As (III) 43: As (V) 586: DMA	160–41,000 Total As
Bile	–	ND: As (III) 43: As (V) 1635: DMA	
Urine	–	ND	
Gastric content	–	ND: As (III) ND: As (V) 1319: DMA	

Data are in μg/L for trivalent arsenic (As [III]), pentavalent arsenic (As [V]), and dimethylarsinate (DMA).
ND, not detected.

10 mL of the following concentrated solution to 950 mL of distilled water: 12 g of sodium phosphate monobasic (NaH_2PO_4) + 3.72 g ethylenedinitrilotetraacetic acid + 41.02 g of sodium acetate + 12.75 g sodium nitrate ($NaNO_3$) + 500 mL distilled water. The mobile phase was adjusted to pH 11 using sodium hydroxide (NaOH, 1 M). Then, 10 mL of ethanol and 1000 mL of distilled water were added. The mobile phase was isocratic. Finally, the residue obtained after digestion was mixed with the mobile phase (1:4) and analyzed by HPLC-ICP-MS. This process was also applied to the calibrators and controls (External Control, G-EQUAS®; Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine of the University of Erlangen-Nuremberg, Schillerstraße, D-91054 Erlangen, Germany).

Results

Arsenic concentrations in antemortem femoral blood samples were very high compared with normal blood arsenic concentrations (2–23 μg/L). The concentration of As (III) was 20 times greater than As (V); no metabolites were detected. In postmortem fluid samples, only As (V) and its metabolites were found. The ante- and postmortem arsenic concentrations were considered to be fatal concentrations based on literature represented in the Table 1. Therapeutic concentrations of oxazepam, nordiazepam, sertraline, meprobamate, and lithium were detected; these were prescribed drugs of treatment. In postmortem samples, only MMA and DMA metabolites and As (V) were identified in liver (Table 2). Significant concentrations of DMA in radial and cubital venous sites were also noted. As toxicological analysis of hair was negative, one can conclude that intoxication was not chronic.

The combination of autopsy findings and histopathological and toxicological analyses indicates that the cause and the manner of death were by a massive acute arsenic intoxication and suicide, respectively.

Discussion

Acute arsenic intoxication is not common and is less frequent than 50–100 years ago. Nevertheless, arsenic poisoning is still an important issue in toxicology. In the past, arsenic was used extensively in agriculture to control parasites and pests. Arsenic exposure in industry is possible during extraction, manipulations and processing of minerals; as well as during the coloring of glass. Organic arsenic is easier to eliminate from the body than pentavalent or trivalent inorganic arsenic. In terms of toxicity, trivalent derivatives are more toxic than pentavalent forms. The inorganic arsenicals, trivalent and pentavalent, are *c.* 100 times more toxic than the organic forms (3).

Arsenic-induced deaths by acute intoxication occur as a result of accidental poisoning (4), medical therapy, or intentional poisoning in cases of homicides and suicides (3). Accidental poisoning appears to be most common in children, whereas intentional and covert poisoning predominates in adults (5,6). Most acute poisonings are fatal (3) and occur following ingestion (7). In this report, the combination of intravenous injection (confirmed by histopathological analysis) and ingestion of arsenic was suspected. This ingestion hypothesis was eliminated for two reasons: the first concerns the toxicological analyses because all the arsenic found in the gastric contents was as DMA and the second concerns the normal gross and histopathological examination of the intestines. The presence of arsenic in gastric content samples could be attributed to normal circulatory absorption or postmortem artifact (7,8). Arsenical poisoning was confirmed by histopathological analysis where the finding of perivasculitis with neutrophils in this case was typical of myocarditis associated with arsenic poisoning (Fig. 2*c*; [3–5]).

Clinical signs of acute arsenic intoxication are usually apparent when the toxicant is administered orally and/or by injection (3,8). Chronic exposure is usually through the skin (9) or via inhalation (10) and results in cutaneous toxicity (e.g., skin cancers) and respiratory problems (7,11,12). Clinical manifestations of acute arsenic poisoning are predominantly gastrointestinal, cardiovascular, neurologic, and renal in nature (7,13–15). Some differences exist between the acute clinical signs and chronic clinical signs, and these differences confirmed the characteristic acute aspects of this case report. Indeed, acute arsenic ingestion may result in rapid death. A garlic-like odor on the breath or in perspiration is suggestive of arsenic poisoning. Death from arsenic is generally caused by circulatory collapse, associated with intense gastroenteritis. In this case, gastroenteritis was not seen, as such, not consistent with an oral route of administration. The most dramatic effects after acute exposure are on the gastrointestinal tract. The corrosive action

TABLE 2—*Toxicological analysis in organ samples.*

Organs	Postmortem	Literature (22) Inorganic Arsenic Concentrations
Liver	28380: DMA 9870: As (V) ND: As (III)	8900–202000 (Total arsenic)
Lung	2780: DMA ND: As (III), As (V)	300–188,000
Kidney	127000: DMA ND: As (III), As (V)	4400–239,000
Injection site: radial venous	910: DMA ND: As (III), As (V)	
Injection site: cubital venous	2290: DMA ND: As (III), As (V)	

Results in μg/kg for trivalent arsenic (As [III]), pentavalent arsenic (As [V]), and dimethylarsinate (DMA). In the right foot injection sites, As (III), As (V), and metabolites were not detected.
ND, not detected.

of arsenic produces extreme gastroenteritis, beginning with burning esophageal pain, difficulty in swallowing, unbearable stomach pain, nausea, projectile vomiting, and explosive diarrhea. The irritant action of arsenic causes bleeding and capillary transudation into the gastrointestinal mucosa, with vesicle formation. Eventually, these vesicles rupture into the gastrointestinal tract, and the tissue produces rice water, bloody diarrhea, and vomitus. Excessive bleeding compromises the circulatory system, and blood pressure progressively decreases (2). In comparison, chronic arsenic exposure at low doses causes a "*milk and roses*" appearance owing to vasodilatation of facial capillaries. Prolonged usage also produces hyperkeratosis, keratosis of the palms and soles, and dermatitis, especially in areas where there is a high concentration of sweat glands. Chronic arsenic poisoning begins insidiously, with the victim complaining of weakness, tiredness, lack of appetite, weight loss, and irritability. More specific characteristics of chronic poisoning are related to effects of arsenic on the integumentary system, causing dark brown pigmentation and a thickening of the keratin layer. Nails thicken and characteristic white bands (Mees' lines) develop above the lunulae (2). These chronic clinical signs were not observed in the patient of this case report.

Survival time following acute arsenic intoxication may be different between oral and intravenous administration. In their review regarding about arsenic intoxication, Gossel and Bricker (2) explained the differences between acute and chronic arsenic intoxication and the survival time as a function of the dose ingested and arsenical form. In this particular case, cardiac and respiratory arrests occurred about 14 h after the injection. Without considering the routes of administration, the dose, and the arsenical form, Jolliffe et al. (7) also noted that a man died 16 h after a significant oral administration of arsenic. With respect to the routes of administration, we could reasonably hypothesize that the direct pathway in the blood circulation increases the risk and the rapidity of circulatory collapse after intravenous administration of arsenic. According to the literature, digestive symptoms are maximal after 8 h, and this is in agreement with this case report. To understand the adverse effects of arsenic via intravenous injection, it is necessary to consider therapeutic use of As for leukemia and hepatocellular carcinoma. Lin et al. (16) reported that arsenic trioxide (As_2O_3) is used for leukemia treatment, with a demonstrated high efficacy in acute promyelocytic leukemia. Most medicinal arsenic trioxide preparations are administered intravenously. Side effects of arsenic trioxide are generally acceptable, including skin reactions, gastrointestinal upset, and reversible increase in transaminases. Arsenic trioxide causes an asymptomatic QT prolongation in most patients. However, if concomitant cardiopulmonary diseases or electrolyte disturbances are present, arrhythmias may develop. Moreover, the dosing of arsenic administered by injection for chemotherapy occurs in a controlled environment (17).

During acute intravenous-induced arsenic poisoning, symptoms are comparable to those observed following oral acute intoxication (7,8,18). Death after acute arsenic administration is generally caused by multiorgan failure (heart, lungs, renal, and digestive) for the two routes of administration (oral and injection). The principal clinical signs are the result of capillary injury that produces vasodilatation, transudation of plasma, and shock (19,20). Accordingly, literature shows a vast range of times to death after arsenic administration (18–20).

Differences between the findings in this case of ante- and postmortem As blood concentrations may be partially explained by the metabolism of arsenic. Arsenic catabolism results in the reduction of As (V) into As (III). The arsenic-containing chemical injected by the woman in this case report was disodium hydrogen arsenic, a

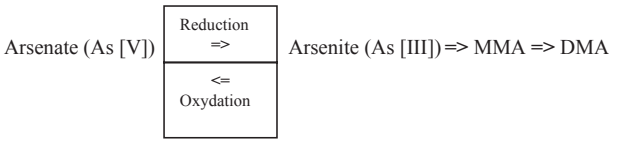

FIG. 3—*Metabolism of arsenic (As [III] and As [V]).*

fungicide. Speciation of the arsenic powder used by the woman revealed that it was pentavalent arsenic (arsenate, As [V]). Owing to metabolism, As (V) was reduced to As (III), which is in agreement with the As (V) and As (III) concentrations observed in the antemortem blood samples. As (III) is then methylated to the metabolites MMA and DMA (21), which is consistent with the postmortem samples (Table 1 and Fig. 3).

The reported lethal doses of acute ingested inorganic arsenic compounds range from 120 to 200 mg of arsenic (2). The acute toxic dose range from 5 to 50 mg, whereas lethal doses of arsenic trioxide range from 70 to 120 mg (2). Toxic effects of inorganic arsenic are observed with values >100 μg/L in the blood (7). Normal blood arsenic concentrations are ranged between 2 and 23 μg/L for Jolliffe et al. (7). The results of the toxicological analyses for arsenic concentrations in this case report exceed the values reported in literature after acute arsenic acute poisoning. Arsenic blood concentrations in cases of massive acute poisoning by ingestion were >160 μg/L (22). The results of postmortem concentrations of arsenic in internal organs of the woman in this case study are in agreement with the literature and consistent with acute arsenic poisoning (Table 2; [22,23]).

To our knowledge, no other case of fatal acute arsenic poisoning by intravenous administration has been reported. Inorganic arsenic is soluble in water, and therefore injection is possible (1). The digestive symptoms reported in this case study were comparable to the first nonfatal case of acute arsenic intoxication by intravenous administration that was reported in 2003 (8). Despite this case report, toxic doses of arsenic toxic doses by intravenous injection are difficult to determine in view of toxicokinetic and individual factors (8).

The source of arsenic used by the woman in this case report should be addressed. Apparently, the young woman had taken it from her brother's bedroom without consent. Her brother had previously been to Madagascar to grow spirulina, and arsenic is a component of a fungicide used in spirulina culture. At the time she took the arsenic-containing compound, she was alone in the house and made the decision to commit suicide. A farewell letter was discovered in her bedroom 1 week later. Moreover, she had syringes and, considering her previous medical history of heroin addiction, she knew how to perform intravenous injections. Histopathological analysis confirmed that intravenous injection was the mode of administration of the toxicant and support the time of injection to be <24 h prior to death. This time scale is in agreement with the police and forensic investigations.

In conclusion, high concentrations of arsenic (As [V] and DMA) were detected in fluid samples, and extremely high concentrations were detected in internal organ samples. In comparison with literature, such high concentrations are consistent with postmortem analysis of specimens from cases of accidental fatal arsenic poisoning (24). Autopsy findings, police investigations, clinical indications together with histopathological and toxicological data are of great importance in the diagnosis of acute arsenic intoxication and in the determination of the cause and manner of death. Finally, to our knowledge, this is the second report describing the biological features of acute arsenic poisoning by injection and the first case report of fatal acute arsenic poisoning by injection.

Conflict of interest: The authors have no relevant conflicts of interest to declare.

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