

Fatal Colchicine Poisoning by Accidental Ingestion of *Colchicum persicum*

A Case Report

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Abstract: Colchicine poisoning can occur not only by taking dosage form but also by ingesting a plant containing colchicine. A 39-year-old man presented to the emergency room with nausea, vomiting, and diarrhea 9 hours after ingestion of wild garlic. Symptoms attributed to food poisoning, and he received supportive cares and discharged. However, he was admitted to the hospital because of severe gastrointestinal presentations 4 hours later. He received treatments based on the diagnosis of acute gastroenteritis. The patient was in a fair condition during 30 hours of hospitalization until he suddenly developed respiratory distress and unfortunately died with cardiopulmonary arrest. The deceased body referred to our legal medicine center for determining cause of death and investigating possible medical staff malpractices. Postmortem examination, autopsy, macropathology and micropathology study, and postmortem toxicological analysis were performed. All results were submitted to the medical committee office for decision. The unknown cause of death was disclosed after determination of colchicine in the plant and botanical identification as *Colchicum persicum*. The committee determined the most probable cause of death as acute cardiopulmonary complications induced by colchicine poisoning and the manner of death as accidental. The medical staff was acquitted of the malpractice.

Key Words: poisoning, colchicine, *Colchicum persicum*, fatality

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LEARNING OBJECTIVES

After participating in this CME activity, the participant should be better able to:

1. Identify the potential sources of colchicine poisoning.
2. Use autopsy, gross pathology, and histopathology findings to determine the cause of fatal colchicine poisoning.
3. Determine the correct cause of death by collecting all evidence related to a death.

Colchicine was approved for the first time in 2009 by the Food and Drug Administration for treating acute gout and familial Mediterranean fever.¹ It is a safe drug when used according to established therapeutic guidelines but causes acute

toxicity and death if ingested in doses that exceed the recommendations.^{2–4} However, colchicine poisoning is not limited to the therapeutics. Colchicine containing plants are more likely to become culprits. Plants of the genera *Colchicum* and *Gloriosa*, both members of the family *Colchicaceae*, contain the natural alkaloid colchicine in toxic amounts.⁵ Colchicine poisoning by ingestion of *Colchicum autumnale* and *Gloriosa superba* was reported frequently in the literature.^{6–10} One of the rare species of the family *Colchicaceae* is *Colchicum persicum*. The name suggests Persia (Iran), but this is also found in Lebanon, Syria, and Iraq to Turkey.¹¹ Here, we report a rare case of fatal colchicine poisoning by accidental ingestion of *C. persicum* instead of wild garlic. To the best of our knowledge, this is the first case report of fatal poisoning with the rare plant containing colchicine (*C. persicum*) in the English literature, and also it is the first report of fatal colchicine poisoning that occurred in Iran. This article will help readers to recognize the potential sources of colchicine poisoning, to use postmortem findings to determine cause of fatal colchicine poisoning, and to determine the correct cause of death by collecting all evidence related to a death.

CASE REPORT

In spring 2011, a married 39-year-old man was presented to the emergency room of the hospital for acute onset of nausea, vomiting, diarrhea, and abdominal pain. On examination, his body temperature was 37.5°C, blood pressure was 130/90 mm Hg, respiratory rate was 12 breaths/min, and pulse rate was 76 beats/min. He was a previously healthy man without any significant medical history as well as drug abuse, alcohol, and smoking. He only reported consumption of wild garlic with his breakfast when he and his friend went to one of Yazd rural areas called Aliabad in about 9 hours ago. Therefore, the physician attributed his presentation to a simple food poisoning and after doing conservative management and following up on 1 hour discharged him. Four hours later, his gastrointestinal (GI) manifestations progressed to severe vomiting and watery diarrhea, and abdominal pain forced him to go to the hospital again. On admission, his vital signs were stable, and there was no significant finding in his electrocardiogram. After blood, urine, and stool specimens were obtained, administration of antiemetic drugs such as metoclopramide and promethazine, intravenous rehydration therapy, and close observation of the patient were performed. Laboratory data results evaluated by the physician were as follows: biochemistry test results of the serum including aspartate aminotransferase 228 U/L (reference range, 34–46 U/L), alanine aminotransferase 90 U/L (reference range, 34–46 U/L), and alkaline phosphatase within the reference value. Hematology tests results showed a mild leukocytosis (white blood cells $13.4 \times 10^3/\mu\text{L}$, as polymorphonuclear leukocytes dominant; reference range, $4\text{--}10 \times 10^3/\mu\text{L}$), hemoglobin 17.8 g/dL, and

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hematocrit 51.3, whereas blood urea nitrogen, creatinine, uric acid, cholesterol, triglyceride, sodium, potassium, glucose, red blood cells, platelets, mean corpuscular volume, and mean corpuscular hemoglobin were within their reference values. The patient's stool specimen was watery and cream color with 15 to 16 white blood cells and 0 to 1 red blood cell and no occult blood and *Escherichia coli* suspicion. Based on the symptoms and laboratory data results, the acute infectious gastroenteritis was diagnosed by the physician, and the patient referred to infectious diseases ward for receiving special treatments and cares. Antibiotic therapy was started with continuing supportive care. Symptoms subsided gradually, and the hospitalized patient was in a fair condition for about 30 hours according to the medical staff reports. During 30 minutes after that time, the patient suddenly developed severe dyspnea and respiratory distress. Immediately, oxygenation with Venturi mask, changing the position to semisitting, and monitoring of vitals signs were provided. Intravenous hydrocortisone was injected. As the situation proceeded to apnea, endotracheal intubation with oxygenation was provided, and cardiopulmonary resuscitation was started. Dopamine, adrenaline, atropine, and sodium bicarbonate were injected. Unfortunately, cardiopulmonary resuscitation attempts for more than 40 minutes failed, and the patient died with the manifestation of cardiopulmonary arrest. After submitting the lawsuit by the patient's family to Yazd Province Court, the deceased's body was referred to Legal Medicine Organization, Center of Yazd, for determining the cause of death and investigating possible medical staff malpractices. Postmortem examination and autopsy were performed about 24 hours after death by a forensic pathologist. The body weight was 85 kg, and height was 170 cm. Obvious rigor mortis was observed in all the joints. Postmortem examination revealed marked pulmonary edema and congestion. Lips were cyanotic. Heart was enlarged with approximate weight of 410 g, and also left cardiac ventricle was hypertrophied, and its free wall thickness was 1.9 cm. Coronary arteries had a mild stenosis. Microscopically, edema was seen in some alveolar spaces. There was no evidence of aspiration. Hypertrophic changes were observed in cardiac myocytes. There were steatotic changes in all centrilobular hepatocytes. Histopathologic abnormalities were not seen in the kidneys. Dura mater had no hemorrhage, and also no cerebral and cerebellar changes were observed. Some parts of the available postmortem specimens including blood, urine, liver, gastric contents, vitreous humor, and bile were sent to the forensic laboratory for toxicological analysis. Toxicological analysis was performed according to the provincial guidelines of Iranian Legal Medicine Organization, Tehran, Iran, as general unknown screening for common poisons in all available postmortem specimens. This involved an enzyme-multiplied immunoassay screen for methadone, morphine, and amphetamine in urine. Vitreous humor was screened for alcohols including ethanol, methanol, and isopropanol with gas chromatography equipped with flame ionization detector. Reinsch test for screening toxic metals including arsenic, antimony, bismuth, selenium, and mercury was performed in stomach content and liver. Colorimetric method (Prussian blue) was used for cyanide detection in stomach content and liver. Both techniques of thin-layer chromatography and high-performance liquid chromatography coupled with a diode array detector (HPLC-DAD) were conducted to screen drugs, poisons, and opiates in prepared extracts of the urine, blood, liver, stomach content, and bile following liquid-liquid extraction methods. However, the results were negative for all tested poisons at the limit of detections. Autopsy and toxicological reports were submitted to the medical committee office of the Legal Medicine Organization, Center of Yazd, Iran, for determining the cause of

death and assessing the possible malpractices. The committee was held by the relevant specialists, deceased person's family and friend, forensic pathologist, medical staff of hospital, and toxicologist. After presenting the case and hearing the statements of the family, the deceased's friend stated that the case consumed some amount of a fresh plant called wild garlic with breakfast, but he refused to also eat the plant because of its bitter taste. The toxicologist suggested the possibility of plant poisoning. Thus, the deceased's friend went to the scene in Aliabad. After recognizing the plant by the friend at the scene, some of the entire plants were pulled out from the soil and taken. The plant specimen was sent to the Research Center of Natural Resources and Agriculture, Yazd, Iran. One specimen was also brought to the forensic laboratory for analysis. At the laboratory, the alkaloid colchicine was found in the extraction of the plant specimen after confirming qualitatively by HPLC. Botanists also identified the genus and species of the plant as *C. persicum*. According to their information, this plant disperses in 3 mountainous rural regions in Yazd Province including Madvar, Adereshk, and Aliabad. By taking all into account, the committee determined the most probable cause of death as acute cardiopulmonary complications induced by colchicine poisoning and the manner of death as accidental. The medical staff were acquitted of the malpractice as well.

METHODS

Identification of Colchicine in the Plant Extract

Colchicine determined qualitatively by reversed-phase HPLC with photo DAD (Smartline 200) (HPLC-DAD) in ambient temperature. Chromatography was performed by using Eurospher 100-5/C18 analytical column (250 × 4.6-mm internal diameter, 5-mm particle size with precolumn) and mobile phase of 100 mM pH 2.3 phosphate buffer/acetonitrile 63/37 in an isocratic manner with the flow velocity of 1 mL/min, injection volume of 20 µL, and total run time of 35 minutes. Amount (~5 g) of the corn of the plant crushed and vortexed with pure methanol. Twenty microliters of the methanolic extract was injected to HPLC-DAD after enough purification with special Millipore filter. Colchicine was eluted in 7.2 minutes of a single run time. Comparison of the UV absorption spectrum peak with standard and also searching in library incorporated into the instrument confirmed the result with peak similarity of 0.9997 (Pragst F, Herzler M, Herre S, et al. *UV Spectra of Toxic Compounds. Database of Photodiode Array UV Spectra of Illegal and Therapeutic, Drugs, Pesticides, Ecotoxic Substances and Other Poisons* [book and CD]. Heppenheim, Germany: Dieter Helm; 2001).

DISCUSSION

Colchicine poisoning presents in 3 sequential and usually overlapping phases: (1) at 10 to 24 h after ingestion, the GI phase occurs with symptoms of nausea, vomiting, diarrhea, abdominal pain, anorexia, electrolyte imbalance, hypovolemia, and peripheral leukocytosis mimicking gastroenteritis; (2) at 24 hours to 7 days after ingestion, bone marrow hypoplasia, profound leucopenia, thrombocytopenia, cardiac arrhythmias, cardiovascular collapse, respiratory distress, hypoxia, pulmonary edema, adult respiratory distress syndrome, renal failure, liver impairment, sepsis, rhabdomyolysis, electrolyte derangements, metabolic acidosis, mental state changes, seizures, peripheral neuropathy, and ascending paralysis occur; generally suggested as multi-organ dysfunction with poor prognosis which potentially results in death; (3) recovery can occur within a few weeks of ingestion.^{5,12,13} However, in cases where a colchicine-containing plant

is accidentally and unknowingly ingested instead of wild garlic, it might be difficult to diagnose colchicine poisoning because on the one hand the reported wild garlic by the patient was considered as safe, and on the other hand the symptoms are possible to be misdiagnosed as food poisoning or acute GI diseases.^{14,15} Our case also misreported the species as *wild garlic*, and hence, there were no attributable findings except the symptoms; the physician suggested food poisoning rather than plant poisoning. One reason can be that the case consumed wild garlic in a rural region that is more likely to be exposed to the microbial contamination because of the possibility of no washing or insufficient washing of the plant when wild garlic was not considered as a poisonous plant. Consequently, colchicine poisoning management and toxicological analysis of the biofluids were not considered at all. Recurrence of GI symptoms after 4 hours, which dragged the patient to the hospital, led the physician to conclude that he was afflicted by acute gastroenteritis especially when supported findings such as mild leukocytosis and stool laboratory data were in favor of that diagnosis. Postmortem findings of fatal colchicine poisoning typically demonstrate multiorgan failure that can be distorted as the cause of death.^{16,17} There are also reports that the autopsy findings have not revealed colchicine poisoning, and thus the deceased's body was buried with the mode of multiorgan failure, but based on circumstantial evidence, the mystery of colchicine fatality was disclosed later.^{4,18} In our postmortem and histopathology findings, the hypertrophied heart was most evident. However, these changes were not justifiable unless colchicine was identified. Interestingly, at first, the hypertrophied heart may suggest previous abnormalities not related to colchicine, but evidence such as reported healthy medical history and the patient's normal electrocardiogram on admission led us to suggest the hypothesis that colchicine probably induced heart hypertrophy. There is also a report of hypertrophied heart related to fatal colchicine poisoning in the literature.¹⁴ Proposed mechanism of this hypertrophy was attributed to the effects of colchicine on myocardial microtubules.^{19,20} Nonetheless, there are reports suggesting sudden cardiac arrest resulting from asystole or ventricular dysrhythmias, which occurred between 36 and 54 hours after ingestion of colchicine despite adequate oxygenation and fluid electrolyte replacement.^{21–23} On the other hand, in our case, pulmonary edema was also evident. We suggest adult respiratory distress syndrome resulted from colchicine as well. Adult respiratory distress syndrome in patients who had colchicine overdose has been frequently reported. The syndrome appeared between 24 and 72 hours. It was characterized by the presence of alveolar pulmonary edema. Most probable mechanisms include direct toxic action of colchicine on pneumocyte microtubules and the inhibition of surfactant production.^{24,25} Thus, we proposed the most probable cause of death as acute cardiopulmonary complications induced by colchicine with possible mechanisms previously stated.

CONCLUSIONS

In patients with food poisoning or gastroenteritis after a plant meal, especially when wild garlic is mentioned, we should always consider possible poisoning with colchicine-containing species, particularly by using autopsy, gross pathology, and histopathology finding to determine the cause of death. Also, in evaluating medicolegal cases, it is important to gather all circumstantial evidence surrounding a death because the exact identity of the perpetrator may be camouflaged in nonspecific autopsy findings and negative postmortem toxicological analyses.

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