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Case Report

Severe accidental colchicine poisoning by the autumn crocus: A case of successful treatment

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Abstract

Background: The common garden plant autumn crocus contains colchicine and its derivatives. Colchicine poisoning causes abdominal cramps and diarrhea within hours. Several days later, multiorgan failure, pancytopenia, and cardiovascular collapse occur.[1,2] Severe colchicine poisoning is associated with high mortality.
Case report: A 63-year-old woman who accidentally ingested an autumn crocus, which contained ~0.38 mg colchicine, had severe vomiting and was taken to an emergency center. She presented with symptoms of gastroenterocolitis within 1 hour of ingestion, and bone marrow hypoplasia with pancytopenia developed on the 3rd day after ingestion. We continued administration of granulocyte colony-stimulating factor (300 μg) for 5 days until we confirmed that the patient's white blood cell count was increasing. Also, there was focal and segmental intestinal ischemia and some cakes of charcoal remained in the intestinal tract. Therefore, we presumed that nonocclusive mesenteric ischemia was caused by hypotension with severe dehydration, although pseudo-obstruction due to the activated charcoal may have been a contributing factor. We were able to promptly intervene to treat paralytic ileus and gastrointestinal edema before anticipated worsening of abdominal compartment syndrome, by conducting open peritoneal drainage. Despite severe poisoning, our patient survived with intensive care. Conclusion: Colchicine intoxication may lead to a sudden and extreme critical course. Therefore, as there is no means to predict prognosis from initial severity of symptoms at onset, we suggest that all patients suspected of colchicine intoxication should be managed in hospital with continuous vital sign monitoring and frequent laboratory testing for at least a few days after ingestion.

Keywords: accidental poisoning; colchicine intoxication; intensive care; myelosuppression; granulocyte colony-stimulating factor

1. Introduction

The common garden plant autumn crocus (*Colchicum autumnale*) contains numerous biologically active substances including colchicine and its derivatives.[1,2] As the leaves and roots of the autumn crocus closely resemble a Japanese herb, people occasionally eat it inadvertently.

Colchicine poisoning causes abdominal cramps and diarrhea within hours. Several days later, multiorgan failure, pancytopenia, and cardiovascular collapse occur.[1,2] Severe colchicine poisoning is associated with high mortality. We report a case of severe accidental colchicine poisoning successfully treated with intensive management.

2. Case Report

A previously healthy 63-year-old woman accidentally ingested an autumn crocus after she had misidentified it as

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wild Japanese ginger. One hour after ingestion, she had several episodes of severe vomiting and was taken to an emergency center with the remaining plant that she had not eaten. It was estimated that she ingested about 11 mg of the autumn crocus, which contained ~0.38 mg of colchicine. The colchicine concentration of the root of the *C. autumnale* was measured by high-performance liquid chromatography at Hokkaido Institute of Public Health. On the day after ingestion, she was transported to our tertiary care center due to hypotension and laboratory evidence of acute liver failure.

Early on the second day, her vital signs were respiratory rate 26 breaths/min, pulse 102 beats/min, blood pressure 97/76 mm Hg, tympanic temperature 36.3°C, and Glasgow Coma Scale 15. Her abdomen was soft but diffusely tender. On echocardiography, the left ventricle wall motion demonstrated diffuse hypokinesis with a left ventricular ejection fraction of 25−30%. Due to her worsening clinical condition, she was electively intubated and placed on mechanical ventilation. She was treated with aggressive fluid resuscitation and administration of norepinephrine, with repeated dose of activated charcoal (AC). Laboratory test results are shown in Table 1. Colchicine concentration in serum was measured by the Poisoning and Drug Laboratory Division (Table 2).

On Day 5, the laboratory test revealed leukopenia and thrombocytopenia. Cefepime hydrochloride and vancomycin were administered for prevention of infection, and 300 μg granulocyte colony-stimulating factor (G-CSF) was administered each day during the subsequent 5 days. An abdominal radiograph was obtained on Day 6, which was consistent with paralytic ileus (Figure 1) and gastrointestinal edema, and the patient developed septic shock, for which we performed an emergency laparotomy (Figure 2) and open abdominal management. Intraoperatively, there was no bowel necrosis, but focal and segmental ischemia of the jejunum, without occlusion of the mesenteric artery and vein. There were some cakes of charcoal. We therefore made a diagnosis of nonocclusive mesenteric ischemia (NOMI). Observation of NOMI can be followed by second-look operation. It was presumed that NOMI was induced by the paralytic ileus from colchicine intoxication, with resultant circulatory insufficiency due to septic shock. After laparotomy, we used polymyxin-B-based cartridges (Toraymyxin) to remove endotoxins for 3 hours.[4,5] Subsequently, we introduced continuous hemodiafiltration for renal indication to treatment of refractory fluid overload.

Table 2
Colchicine concentration in the serum.

(d)	2	3	4	5	6	7	8	9	10	11
Colchicine (ng/mL)	2.3	1.6	1.2	1.2	1.3	1	0.5	0.41	0.19	N.D.

Colchicine concentration in serum was measured by the Poisoning and Drug Laboratory Division.
The maximum concentration of colchicine in the blood was 2.3 ng/mL on Day 2. Despite this blood concentration being less than the toxic concentration identified by Molad,[3] the patient's course was severe. N.D. = Not Detected.

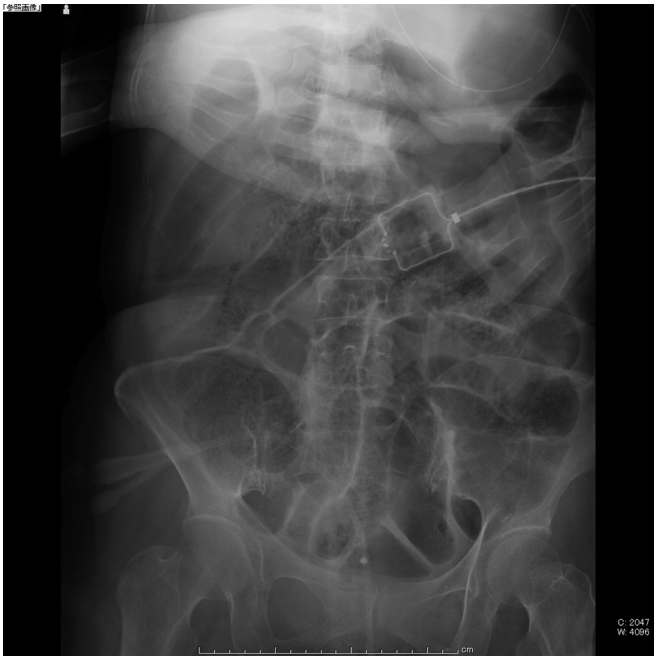

Figure 1. Abdominal X-ray showing paralytic ileus on Day 6.

On Day 9, her myelosuppression improved (Figure 3). She made a full recovery from septic shock and was successfully weaned from mechanical ventilation on Day 13. She required continuous hemodiafiltration and was switched to intermittent hemodiafiltration on Day 18, and then subsequently weaned from renal replacement therapy completely on Day 23. On Day 34, the patient was transferred to a rehabilitation facility with biochemical and hematological laboratory values within normal ranges.

Table 1
Laboratory findings after *Colchicum autumnale* intoxication.

	Unit	Normal range	Measured value										
(d)			1	2	3	4	5	6	7	8	9	10	33
AST	IU/L	11−39	46	374	754	436	223	86	47	21	24	30	16
ALT	IU/L	5−40	24	176	354	233	177	104	80	48	32	36	23
CRP	mg/dL	0.0−0.3	0.08	7.45	10.84	7.97	15.16	22.35	41.85	42.67	33.7	20.38	0.34
CRE	mg/dL	0.45−0.94	0.77	0.83	1.1	0.8	0.5	0.4	0.8	0.8	1.1	1.4	0.8
UN	mg/dL	6.0−20.0	14.6	18.8	25	24	15	11	24	30	39	51	3.6

Laboratory test revealed leukopenia and thrombocytopenia on Day 5 and the patient developed septic shock on Day 6. Myelosuppression improved on Day 9.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRE = creatinine; CRP = C-reactive protein; UN = urea nitrogen.

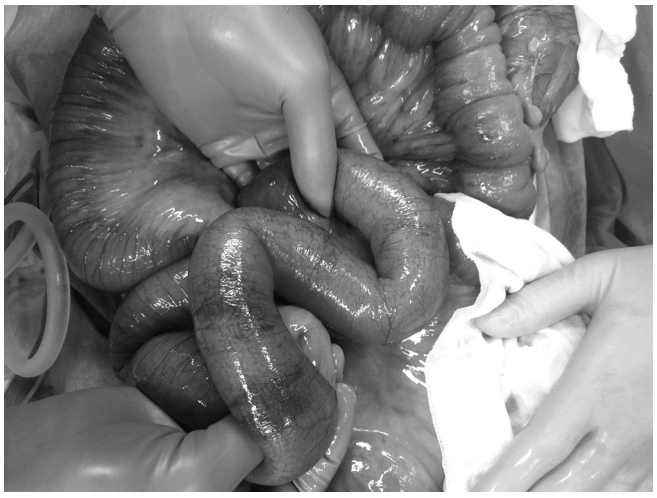

Figure 2. Intraoperative findings. There was no bowel necrosis, but focal and segmental ischemia of the jejunum, without occlusion of the mesenteric artery and vein.

and is characterized by life-threatening complications such as circulatory failure, arrhythmias, renal failure, hepatic failure, respiratory distress, bone marrow depression, and coagulopathy. Complications such as gastrointestinal hemorrhage and disseminated intravascular coagulation frequently occur. The third phase of colchicine poisoning occurs 7−21 days after ingestion, which is characterized by rebound leukocytosis, alopecia, and possibly other complications including delirium, stupor and coma, and seizures.[6] Our patient presented with symptoms of gastroenterocolitis within 1 hour of ingestion, and bone marrow hypoplasia with pancytopenia developed on the third day after ingestion.

Despite severe poisoning, our patient survived with intensive care. To investigate the relationship between poisoning symptoms and severity, a literature search was conducted by searching the PubMed database between 1993 and January 2013 using keywords “colchicine” and “poisoning”. This search identified 186 papers. This list was manually screened for papers relating to colchicine poisoning in humans, the

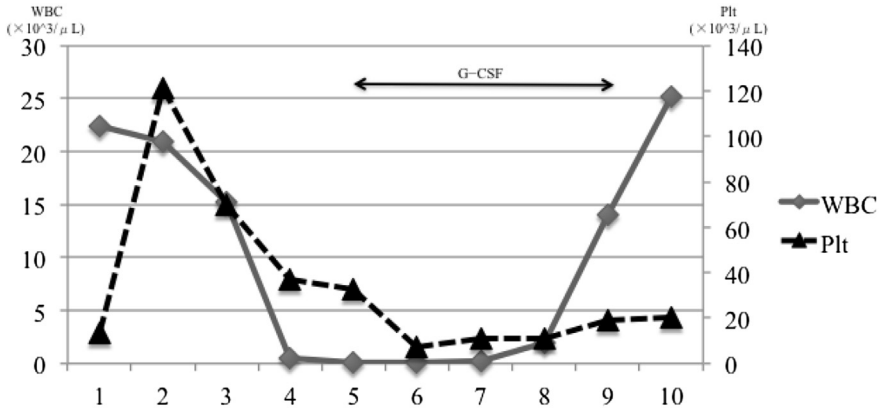

Figure 3. White blood cell (WBC) and platelet response to G-CSF administration. We administered 75 μg G-CSF once (Day 5), however, 300 μg G-CSF was administered once daily during the subsequent 3 days because WBC count decreased rapidly. After 5 days (Day 9), WBC count began to increase. Platelet count had not increased on Day 10. G-CSF = granulocyte colony-stimulating factor; Plt = platlet.

3. Discussion

Colchicine binds to tubulin, thereby preventing its polymerization into microtubules. Microtubule deficiency leads to impairment of many cellular functions.[6] Tissues with high mitotic activity are preferentially affected. As an antimitotic agent, colchicine blocks mitosis in metaphase, preventing DNA synthesis.

In toxic doses of colchicine, the toxin binds to specific regions on tubulin and can interfere with microtubule structure and function.[6] These effects occur in all cells, which explain the multiorgan toxicity seen with poisoning.[7] Organ systems with the highest cell turnover rate (bone marrow, gastrointestinal tract, and hair follicles) are the most vulnerable and readily affected.

The clinical course of acute colchicine poisoning generally occurs in three phases.[6] The first phase is characterized by vomiting and diarrhea, which generally start 4−12 hours after ingestion. The second phase begins 2 or 3 days after poisoning

mechanism of toxicity, or its clinical management. This yielded a total of 78 papers. Seventeen of the papers were related to accidental plant ingestion. There was considerable variation among all factors in the poisoning, including time to symptom onset, age, amount ingested, and method of poisoning. However, we did not find any association between poisoning severity and these factors.[7−21] In colchicine poisoning, there is no clear correlation between the amount of plant matter ingested and serum concentrations.[6,22] Usually, toxic effects do not occur with concentrations <3 ng/mL.[21] Moreover, the concentration of colchicine in blood and bile is poorly correlated.[8,22] In our case, the maximum concentration of colchicine in blood was 2.3 ng/mL. Despite this blood concentration being less than the toxic concentration identified by Molad,[3] the patient's course was severe. Due to its unpredictable outcome, Brncić et al[9] recommend that all patients suspected of colchicine intoxication should be managed with intensive care monitoring and support, irrespective of the actual degree of poisoning.

The Japanese poison control center recommends that AC should be given every 6 hours to reduce intestinal absorption of colchicine. Putterman et al stated that multiple-dose activated charcoal (MDAC) therapy should be considered because of enterohepatic recirculation during colchicine poisoning.[23] However, the adverse effects include intestinal obstruction and pseudo-obstruction after repeated doses of AC in the presence of dehydration. In colchicine poisoning, gastrointestinal irritant effects such as vomiting and diarrhea occur and may lead to severe hypovolemic shock. Severe hypovolemic shock may cause NOMI. In our case, there was also focal and segmental intestinal ischemia and some cakes of charcoal remained in the intestinal tract. Therefore, we presume that NOMI was caused by severe hypovolemic shock, although pseudo-obstruction due to the AC may have been a contributing factor. These factors point to a need for careful monitoring of warning signs of intestinal ischemia during management with MDAC therapy. We were able to promptly intervene to treat paralytic ileus and gastrointestinal edema before the anticipated worsening of abdominal compartment syndrome, by surgical abdominal decompression.

In this case, granulocytopenia was improved by the administration of G-CSF. We continued administration of G-CSF (300 μg) for 5 days until we confirmed the patient's white blood cell count was increasing. G-CSF can be an effective supportive care measure for granulocytopenia induced by colchicine intoxication, as it is thought to help prevent septicemia. Finkelstein et al[7] reported that G-CSF should be considered if there is myelosuppression. Critchley et al successfully treated a patient with severe colchicine poisoning using 600 μg G-CSF. When G-CSF is used, daily monitoring of the patient's hematological status is strongly recommended.[24]

In conclusion, colchicine intoxication may lead to a sudden and extreme critical course. Therefore, as there is currently no means to predict prognosis from initial severity of symptoms at onset, we suggest that all patients suspected of colchicine intoxication should be managed in hospital with continuous vital sign monitoring and frequent laboratory testing for at least a few days after ingestion. Caution must be exercised with the use of MDAC, as it may cause or accelerate intestinal ischemia. Lastly, G-CSF can be an effective therapy in the face of myelosuppression after colchicine poisoning.

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