CASE REPORT

Acute Fulminant Hepatic Failure due to Colchicine – a rare manifestation of *Gloriosa superba* poisoning.

ANANDHI D, KNJ PRAKASH RAJU, BALAJI SHAH BDS, ANUUSHA SS.

Department of Emergency Medicine, Jawaharlal Institute of Postgraduate Medical Education & Research, Puducherry, India.

Abstract

Background: Patients presenting to Emergency department following consumption of toxic substances is not an uncommon phenomenon globally. It becomes essential for the Emergency physicians to have in-depth knowledge of all the toxic products available in their locality. In rural parts of South India, the most common method of poisoning is by consumption of pesticides, followed by plant poisons, because of its easy availability. *Gloriosa superba* is an important medicinal plant growing in several parts of Southeast Asia. All parts of this plant contain several alkaloids including colchicine with the highest concentration in seeds and tubers. Acute intoxication following ingestion of *G. superba* is indistinguishable from colchicine overdose.
Clinical presentation: The symptoms of intoxication can be classified in three phases. Phase 1:(2-24 hours) early gastrointestinal symptoms mimicking gastroenteritis, volume depletion, hypotension, peripheral leucocytosis; Phase 2:(24 to 72 hours) mental status changes, oliguric renal failure, hematopoietic problems, electrolyte imbalance, acid-base disturbance, shock, bone marrow suppression, liver failure, ARDS, arrhythmias, cardiovascular collapse, encephalopathy and neuromuscular involvement; and Phase 3:(1-3 weeks) Recovery typically occurs within few weeks of ingestion but with rebound leucocytosis and alopecia.
Case report: We present a patient who ingested *Gloriosa superba* tubers with suicidal intent and developed acute fulminant liver failure a week after ingestion. Two weeks later, he also developed alopecia. Liver functions gradually improved and normalized after three weeks of hospitalisation. He was provided supportive treatment and he improved remarkably. At discharge, total bilirubin was 1.3 mg/dL, direct bilirubin 0.6 mg/dL, serum urea 15mg/dL and serum creatinine 0.9 mg/dL. On follow-up visits, alopecia showed an improving trend.
Conclusion: Colchicine exerts a multiorgan toxicity. Acute fulminant hepatic failure can be a life threatening manifestation of *Gloriosa superba* poisoning. Hepatic failure can be due to colchicine induced direct hepatic injury with cytolysis. Management is essentially supportive with anecdotal reports showing benefit in plasmapheresis.

Key words: Poisoning, Liver Failure, Drug Induced Liver injury, Toxicology

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INTRODUCTION

Gloriosa superba, a plant belonging to the family *Colchicaceae*, grows in the tropical climates of Africa, Asia (including India, Sri Lanka, Malaysia, and Burma), Australia and Pacific islands. Names in other languages include flame lily, glory lily (English), Niyagala (Sinhalese), Karthigaipoo, Kalappaikilangu, Senganthal (Tamil), Kalihari (Hindi), Gowrihoo (Kannada) and NagatiGadda (Telugu). [1, 2] It is the state flower of Tamil Nadu and national flower of Zimbabwe. [1] Gloriosa superba has diverse medicinal applications and due to over-exploitation, it is now facing local extinction. It has been affirmed as a critically endangered plant by IUCN (International Union for Conservation of Nature) and has been placed in "red data book". [3] It is cultivated in Tamil Nadu and Andhra Pradesh for its medicinal value. Glory lily is used in traditional medicine (including Ayurveda) for the treatment of acute gout, rheumatism, ulcers, intestinal worms, infertility and as an antidote for snake bite. [4] The seeds, tubers and leaves of *G. superba* have antimicrobial, anthelminthic, antioxidant activity and anticoagulant properties. [5] All parts of this plant, especially the seeds and tubers, contain toxic alkaloids, including colchicine and gloriosine. [4, 6] This plant is considered as colchicine sources for the chemical constituents of medicine industry. Colchicine is used in the acute treatment and prevention of gout and is used in other disorders, including amyloidosis, Familial Mediterranean Fever, Behcet's disease, pericarditis, arthritis, pulmonary fibrosis, vasculitis, biliary cirrhosis, pseudogout, certain spondyloarthropathies, calcinosis and scleroderma. [7] It is no surprise that the pharmacological benefits of *G. superba* have been attracting great interest. Lethal dose is about 0.8 mg/kg and fatalities usually occur 2-7 days post ingestion secondary to multiorgan failure. [8] In the western province of Sri Lanka,

*Correspondence to: Anandhi D, M.D, Assistant Professor, Department of Emergency Medicine & Trauma, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India. Pin: 605006
Mail: anandhideva1@gmail.com, Cell: 91-9626064984

Gloriosa superba is responsible for 44% of plant poisonings with a 15% case fatality rate. [9]

CASE PRESENTATION

A 40 year old male, with an intention of deliberate self-harm, ingested an unknown number of glory lily tubers (Image 1) which he availed nearby his residence. He was initially managed at a nearby hospital for 24 hours and then was referred to our centre. He presented with nausea, vomiting, abdominal pain and loose stools. His pulse rate was 130/min, blood pressure 90/60 mmHg and room air saturation 94%. Systemic examination was normal. EKG showed sinus tachycardia. Laboratory investigations revealed serum potassium of 1.67 mEq/L, serum sodium 133 mEq/L, urea 56 mg/dL and serum creatinine 1.3 mg/dL. Baseline hemogram and liver function tests were within normal limits. He was treated with gastric lavage, fluid resuscitation and intravenous potassium replenishment. Serum potassium normalised after 3 days of hypokalemia management. A week later, he developed brownish discolouration of teeth (Image 2), epistaxis, hemoptysis, and jaundice with yellowish discolouration of sclera (Image 3) and flapping tremors. Repeat complete blood counts exhibited hemoglobin 12.6 g/dL, WBC count $18.4x10^9$/L and platelet count $19x10^9$/L. Total bilirubin was 10.64 mg/dL, direct bilirubin 6.90 mg/dL, indirect bilirubin 3.68 mg/dL, SGOT 21.2 U/L, SGPT 34 U/L, alkaline phosphatase 142 U/L and prothrombin time 35 seconds with international normalised ratio 1.6. His Hepatitis B status was negative. Liver sonography showed mild fatty liver and kidney sonography was normal. He required four units of platelets and eight units of fresh frozen plasma transfusion. He was managed supportively for hepatic encephalopathy. During in-hospital stay, he also developed generalised, non-patchy alopecia mainly involving fronto-temporal region of the scalp. Liver functions gradually improved and returned to normal range after three weeks of hospitalisation. At discharge, total bilirubin was 1.3 mg/dL, direct bilirubin 0.6 mg/dL, serum urea 15mg/dL and serum creatinine 0.9 mg/dL. On follow-up visits, alopecia showed an improving trend.

DISCUSSION

The toxic manifestations of *Gloriosa superba* poisoning is varied, with multi organ system involvement. Acute fulminant hepatic failure is an uncommon presentation of this toxic tuberous plant. We report a case who developed acute fulminant hepatic failure following *Gloriosa superba* ingestion.

The active principle constituents of *Gloriosa superba* plant include highly active alkaloids such as colchicine, gloriosine, superbrine (a glycoside), chelidonic acid and salicylic acid. [4] Colchicine is rapidly absorbed from the intestine and undergoes significant first-pass hepatic metabolism. The metabolites undergo enterohepatic circulation and are subsequently excreted in stools, leading to extended exposure of the intestine to toxic effects. Renal clearance accounts for about 10-20% of colchicine excretion. [1]Individuals with end-stage kidney disease and liver cirrhosis have elimination half-lives that are prolonged up to ten fold. Colchicine exerts its primary toxicity by binding to tubulin and interfering with

Image 1. Gloriosa superba tuber.

Image 2. Showing brownish discolouration of right incisors teeth

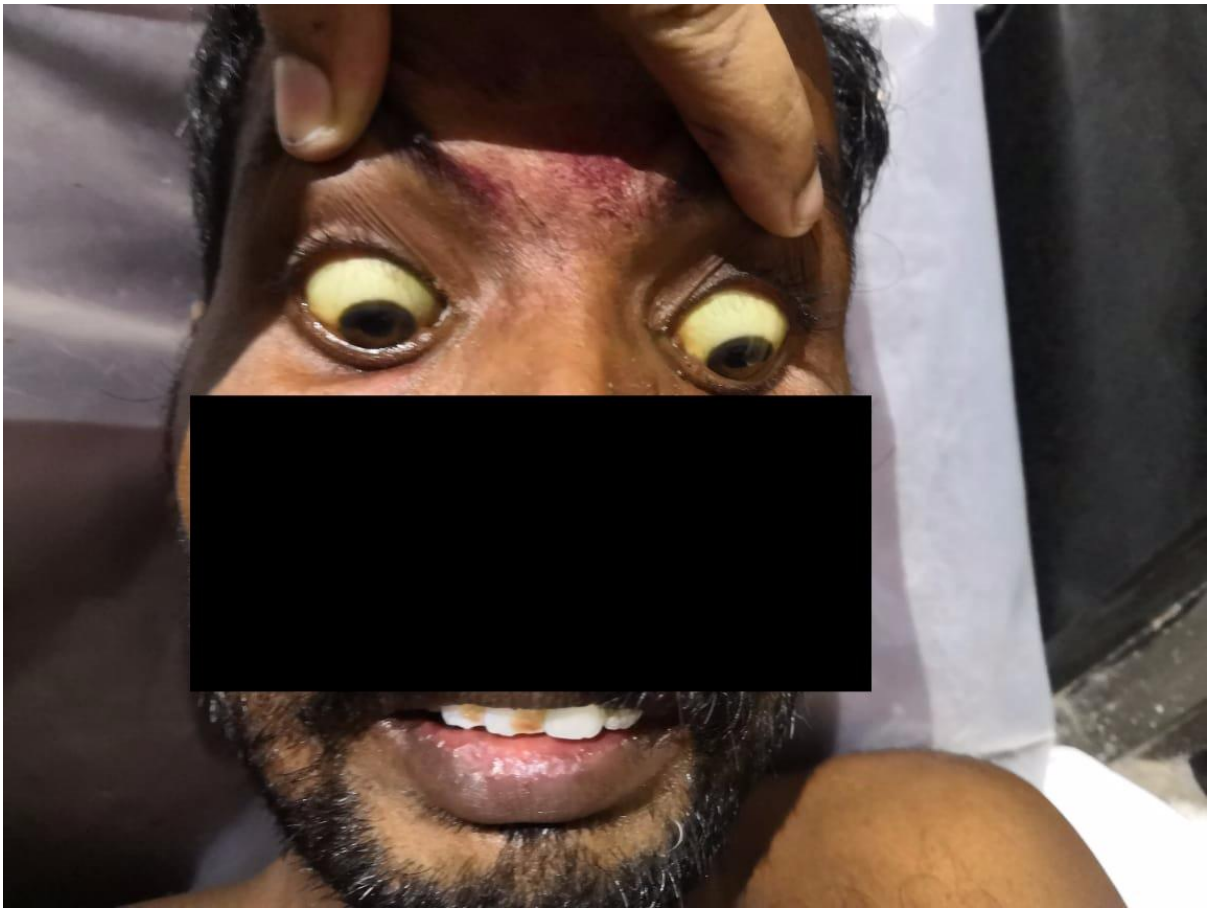

Image 3. Showing jaundice with yellowish discolouration of sclera

microtubule structure and function. [7] It inhibits microtubule formation and polymerization by binding to tubulin, one of the main constituents of microtubules. The binding is reversible and the half-life of colchicine-tubulin complex is 36 hours. Availability of tubulin is essential to mitosis, and therefore colchicine effectively functions as a "mitotic poison" or spindle poison. [10] Therefore, cells with high turnover and high metabolic rate such as intestinal epithelium, hair follicle, bone marrow cells, etc. are highly susceptible to the toxic effects of glory lily. [6, 11] Toxic effects usually do not occur with concentrations less than 3ng/mL. Colchicine crosses the placenta and is secreted in breast milk, but it is not dialyzable. [7]

A choleriform syndrome (epigastric pain, watery diarrhea, vomiting, fever and dehydration) should raise the suspicion of colchicine poisoning. [12] Toxic manifestations occur after a delay of 2-12 hours after oral ingestion. The symptoms of intoxication can be classified in three phases. Phase 1: (2-24 hours) early gastrointestinal symptoms mimicking gastroenteritis, severe volume depletion, hypotension resulting from severe vomiting and diarrhea, and peripheral leucocytosis; phase 2: (24 to 72 hours) widespread organ system dysfunction, particularly the bone marrow, mental status changes, oliguric renal failure, hematopoietic problems, electrolyte imbalance, acid-base disturbance, shock, bone marrow suppression, infectious complications, liver failure, coagulation disorders with diffuse hemorrhage, acute respiratory distress syndrome, arrhythmias, cardiovascular collapse, encephalopathy, rhabdomyolysis; cardiogenic shock may result in death within the first 72 hours and phase 3: (1-3 weeks) Recovery typically occurs within few weeks of ingestion but with rebound leucocytosis, alopecia, myopathy, neuropathy or myoneuropathy. Electrolyte and acid-base imbalances such as metabolic acidosis, hyponatremia, hypocalcemia, hypokalemia, hypophosphatemia, and hypomagnesemia have been reported. [7,8, 13] Our patient also followed the same course of manifestations. He had vomiting, loose stools on day 1 and electrolyte imbalances on days 2 and 3, but liver failure and thrombocytopenia developed only after a week of ingestion. After 2 weeks, he noticed generalised non patchy alopecia, mainly involving fronto-temporal region of the scalp.

In a Sri Lankan prospective study of patients with Niyagala poisoning, 93.9% developed acute gastrointestinal symptoms; 21.2% had cardiotoxic effects; 9% developed respiratory failure; 15.2% had neurological and bleeding manifestations; and 6% had acute kidney injury. Hypokalemia was observed in 48.5%, leukopenia in 15.2% and anemia in 12.1% patients. Alopecia was observed in 12.1% patients as the long term effect. [14]

Colchicine toxicity is associated with the development of dysarrhythmias and cardiac arrest. Complete AV block has been reported in a child who ingested 0.4-0.5 mg/kg. Sudden cardiovascular collapse from colchicine typically occurs between 24-36 hours after ingestion. Adult Respiratory Distress Syndrome (ARDS) occurs with colchicine toxicity. The cause is not well understood, but probably related to several factors, including respiratory muscle weakness, multiorgan failure and direct pulmonary toxicity. Respiratory failure is due to the paralysis of intercostal muscles rather than the direct depression of the respiratory centre by colchicines. Our patient did not manifest any cardiac or respiratory findings. Neurologic effects, including delirium, stupor, coma, delayed encephalopathy, and seizures are reported in colchicine poisoning. Our patient developed grade 2 hepatic encephalopathy, which was managed conservatively. Myopathy, neuropathy and a combined myoneuropathy result from both long-term therapy and acute poisoning. Patients may present with proximal limb weakness, distal sensory abnormalities, distal areflexia, and nerve conduction problems consistent with an axonal neuropathy. Other reported complications include bilateral adrenal hemorrhage, disseminated intravascular coagulation, pancreatitis, and liver dysfunction. [7]

Hypovolemic shock, rhabdomyolysis, multi-organ failure and possible direct toxicity on proximal renal tubules are all the proposed mechanisms of acute kidney injury. [15] Colchicine may exert direct hepatic toxicity with moderate cytolysis and this may reduce the production of clotting factors. Histological features include necrosis and steatosis of hepatocytes. There may be increase in alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and decrease in coagulation factors. Thus bleeding tendencies may occur associated with high prothrombin time (PT) /international normalized ratio (INR). Bleeding manifestations may include malena, hematemesis, per rectal bleeding, per vaginal bleeding and haematuria. [14] Our case had fulminant hepatic failure on week 2, the probable pathophysiology can be due to direct hepatic toxicity and cytolysis by colchicine.

Hyponatremia is usually attributed to severe diarrhea and can be managed with volume replenishment. Persistent hyponatremia despite volume replacement should alert the clinician of SIADH, a well-recognised rare complication of *Gloriosa superba* poisoning. Tolvaptan may be a life-saving therapy under such circumstances. [16]

Alopecia, which is usually reversible, is a well-described complication that occurs 2-3 weeks after poisoning in survivors. Dermatologic complications range in severity from epithelial cell atypia to toxic epidermal necrolysis. Although uncommon, poisoning from IV colchicine administration has occurred. Toxic dose is lower compared to that of oral ingestion.

Management is mainly supportive, which includes IV fluid replacement, vasopressor use, hemodialysis for acute kidney injury (not for toxin removal), antibiotics for suspected secondary infection, colony-stimulating factors, and adjunctive respiratory therapy. [7] The first step of treatment is timely gastrointestinal decontamination with activated charcoal. Very large, recent (<60 minutes) ingestions may warrant gastric lavage. Administration of granulocyte colony-stimulating factor might help in combating hematological cell deficiency. [13] Demirkol *et al* had reported a case of colchicine intoxication which was successfully managed with plasma exchange. They hypothesized that plasma exchange might be beneficial by facilitating elimination of colchicine. [17] Currently, there is no existing evidence for the use of intravenous lipid emulsion in colchicine toxicity. [18] Colchicine specific Fab fragments was successfully used in severe colchicine toxicity, however its use is limited by its high cost and less availability. [19] Prognosis is usually related to the dose ingested. Occurrence of cardiogenic shock indicates a poor prognosis. If the patient has recovered from aplasia, and not developed ARDS or systemic infectious complications, prognosis is usually good. At the early stage, death is due to cardiogenic shock or ARDS. Death during days 3-10 may be due to hemorrhagic or infectious complications at the stage of bone marrow aplasia. Post mortem examination of colchicine-poisoned patients reveals high concentrations with the bone marrow, testicles, spleen, kidney, lung, brain, and heart. [7]

In our case, initially we could not identify the toxic tuber. The patient's relatives at his residence shared the pictures of the plant to the treating physician's mobile phone. Exact identification of the toxic plant helped in appropriate management of our patient. Colchicine specific Fab fragments may be used in severe toxicity. But due to lack of availability and high cost, it was not provided to our patient.

CONCLUSION

Physicians should be aware of varying clinical manifestations of *Gloriosa superba* toxicity. There is a multi-organ system involvement in *Gloriosa superba* poisoning such as gastrointestinal tract, heart, lungs, kidneys, brain, liver and hemopoietic system. Acute fulminant hepatic failure is an uncommon manifestation of gloriosa superba poisoning. Liver failure can be managed conservatively, though liver transplantation may be necessary in extreme cases.

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