Acute Mushroom Toxicity

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INTRODUCTION

There are approximately 100 species of mushrooms that are poisonous amongst more than 5000 species identified, and there were greater than 8000 mushroom poisonings reported in the United States in 2001 (3). The majority of fatal poisonings are caused by Amanita phalloides (death cap) or Amanita verna (destroying angel) found mainly in the Pacific Northwest and eastern United States. There are multiple toxins responsible for the destructive effects including alpha-amatoxin and phalloidin. Alpha-amatoxin is thermostable and not inactivated by cooking. The amatoxin travels via the enterohepatic circulation to the hepatocytes where it stops the production of messenger RNA and protein synthesis resulting in cell necrosis. The toxin phalloidin interferes with polymerization of actin and disrupts cell membranes and is responsible for the severe gastroenteritis that occurs before the hepatic and central nervous system injury (3).

A period of 6-20 hours passes after the ingestion of a toxic mushroom before the onset of initial symptoms including severe abdominal pain, vomiting, and diarrhea. This is followed by hepatocellular jaundice and renal failure over the next 24 to 48 hours, while confusion, delirium, convulsions and eventual coma occur by 72 hours (2,3).

This case report presents a rare cause of acute liver toxicity. The differential diagnosis of markedly elevated transaminases above 1000 IU/L includes acute viral hepatitis, shock liver and drug/toxin induced liver injury. It is extremely important to take a complete history of a patient including going into depth of the social history as it can provide clues to the etiology of liver disease.

CASE PRESENTATION

A 65 year old Caucasian male presents with a one day history of multiple episodes of bilious emesis and non-bloody diarrhea with symptoms progressing to total body cramps, jaw pain, and expressive aphasia. Past medical history includes Non-Hodgkin’s Lymphoma and Prostate cancer. Social history includes tobacco use greater than 70 pack year and 2 drinks per day for the last 2-3 years. Pertinent physical exam findings include mild scleral icterus and diffuse tenderness to palpation of the abdomen. Initial labs showed total bilirubin of 4.5, direct bilirubin of 2.6, alkaline phosphatase of 128, AST of 4442, ALT of 7870, total protein of 6.4, albumin of 3.7, lactate of 5.5, and coagulation indices showed PT of 39.1, PTT of 69.1, and INR of 5.8. These labs indicate a combination of synthetic liver dysfunction, hepatocellular and cholestatic damage. After further inquiry of social history, it was found that patient was a
mushroom forager and ate five mushrooms that resembled amanita phylloides on the day of admission. During the hospitalization, patient became combative and encephalopathic requiring intubation for airway protection. The patient was initially started on Penicillin G and intravenous Silybum marianum but his confusion persisted along with elevations in his liver function tests. Eventually this patient required a liver transplantation with subsequent improvement in laboratory tests and mental status.

**DISCUSSION**

There are three main families of mushrooms which contain lethal amatoxins including Amanitaceae, Cortinariaceae, and Agaricaceae. The toxins of the genus Amanita include amatoxins, phallotoxins, and virotoxins. The phallotoxins are poorly absorbed, and are responsible for gastrointestinal symptoms while exerting their effects between 1-2 hours. On the other hand, Amatoxins take longer to act between 10-15 hours post-ingestion and are more toxic. These toxins are resistant to heat and freezing and thus cannot be denatured by cooking or digestive enzymes (4).

The amatoxin are present mainly in the pileus, ring, and stem of the basidiome (or fruiting body). The lethal dose of amatoxin ingestion is <0.1 mg/kg of body weight and a mature mushroom can contain a fatal dose of 8-12 mg. The mechanism of action of amatoxins includes inhibiting protein synthesis in enterocytes, hepatocytes, and renal proximal tubular cells. More specifically, the organic anion polypeptide transporter located in the cytoplasmic membrane binds to the subunit of RNA polymerase II transcription, leading to interference with DNA and suppression of RNA production. As a result, protein synthesis is halted and cell death ensues (4).

Amanita poisoning presents with four various clinical stages: 1) the incubation stage occurs between 6-12 hours after ingestion where patients are asymptomatic; 2) the gastrointestinal stage can occur up to 24 hours post ingestion and is characterized by abdominal pain, nausea, vomiting, and diarrhea which can lead to dehydration and shock; 3) the cytotoxic stage is characterized by clinical improvement after 24-48 hours post ingestion followed by a worsening of renal or liver function; 4) the final phase can begin suddenly with coagulopathy, hepatic encephalopathy, hypoglycemia, and development of fulminant hepatic failure combined with acute renal failure (4).

A retrospective analysis of 294 cases of mushroom poisoning by Eren et. al showed that the most common initial symptom in 84.8% of adults was nausea and vomiting with additional symptoms including fatigue, abdominal pain, dizziness, diarrhea, headache, and loss of consciousness. Additionally, 37.7% of the patients had laboratory abnormalities. Specifically, 8.1% of cases showed increased levels of AST and ALT where AST values were between 2075-3464 U/L and ALT values between 2345-4048 U/L for the patients who died from mushroom poisoning. This specific analysis showed an important relationship between mortality and liver
enzyme levels and shows that level of liver enzymes are a good prognostic marker of mushroom poisoning (2).

Mortality due to mushroom poisoning can be high as 20% in adults and 50% in children. Risk factors that lead to a higher mortality risk include age less than ten, female gender, short interval between ingestion, onset of diarrhea (less than 8 hours), severe coagulopathy, severe hyperbilirubinemia, elevated creatinine, and a rapid increase in prothrombin time. Initial therapy consists of gastric lavage, intensive fluid resuscitation, and activated charcoal with a cathartic to remove all remaining stomach contents and any toxin from enterohepatic circulation. After activated charcoal, the remaining therapy is pharmacological including Penicillin G and Silybum marianum (1,5).

Milk thistle (Silybum marianum) has been investigated for use as a cytoprotectant, an anticarcinogen, and as supportive treatment for liver damage from Amanita phalloides poisoning. Silymarin, the active ingredient, undergoes enterohepatic recirculation leading to higher concentrations in liver cells as compared to the serum, and inhibits the binding of toxins in the mushroom to hepatocytes. The cytoprotective effects of Silymarin include acting as an antioxidant and free radical scavenger. Additionally, Silymarin can enter the nucleus and act on RNA polymerase leading to increased ribosomal formation and thus increased protein synthesis. This specific action leads to repair of damaged hepatocytes and restoration of normal liver function (6).

A study by Feher et. al showed that of the 36 patients with chronic liver disease who received Legalon, a proprietary product standardized to contain 70 to 80 percent Silymarin, there was a return to normal levels of bilirubin, aspartate transaminase, and alanine transaminase levels along with normalization in histology. These effects were not duplicated in the placebo group (6). In addition, a study done by Salmi et. al which randomized 106 patients with mild acute and subacute liver disease to receive Silymarin or placebo showed a statistically significant decrease in transaminase levels in the study group after four weeks (6).

Liver transplantation must be considered in patients with hepatic encephalopathy with elevations in liver function tests and is the treatment of choice for fulminant liver failure in the absence of contraindications. Due to the limited availability of donor organs, only approximately 10% of patients with fulminant liver failure receive transplants. Therefore good ICU care is an integral component of therapy while optimizing medical management for these patients complemented by the use of extracorporeal liver assist devices. Stange and Mitzner developed a blood detoxification method for protein-bound substances known as the MARS system which consists of an albumin rich closed-loop circuit with two areas of depuration. This system allows for the replacement of the liver’s detoxification function. Substances that are removed by the MARS include ammonia, bilirubin, free fatty acids, and aromatic aminoacids (1).
CONCLUSION

The diagnosis of acute mushroom poisoning must be considered in patients who present with symptoms of nausea, vomiting, and diarrhea along with laboratory studies showing transaminases greater than 1000 IU/L, hyperbilirubinemia, and coagulopathy. It is imperative to obtain a complete history on all patients including a social history because all information can help identify the final diagnosis. Patients can be started on Penicillin G and intravenous Silybum marianum to attempt to normalize laboratory values back to baseline and improve mental status. However, if liver function tests continue to rise and patients become encephalopathic, then a liver transplantation would be treatment of choice.


