A Case of *Amanita phalloides* Poisoning that Avoided Liver Transplantation

Tomoyuki Hongo, MD, Matthew Zheng, MD, Mark Malamood, MD, and Steven K. Herrine, MD

ABSTRACT

We describe a 49 year old male admitted with acute liver failure from likely *Amanita phalloides* poisoning, treated with NIH clinical trial protocol.

CASE PRESENTATION

The patient is a 49 year old male with a history of chronic untreated hepatitis B and intraductal papillary mucinous neoplasm of the pancreas who initially presented to an outside hospital (OSH) with intractable nausea and non-bloody, non-bilious vomiting that began twelve hours after eating seven gray-white mushrooms from his backyard.

On initial presentation to the OSH, his hepatic function panel and coagulation markers were within normal limits. He was treated symptomatically with intravenous (IV) fluids and anti-emetics. Subsequently, he developed significantly elevated serum aminotransferases. On day 4 after ingestion, he was transferred to our hospital with concern for fulminant hepatitis and consideration for liver transplantation. On transfer, his aspartate aminotransferase (AST) was 4217 U/L, alanine aminotransferase (ALT) was 7385 U/L, alkaline phosphatase (ALP) was 105 U/L, total bilirubin (Tbili) was 5.0 mg/dL, and international normalized ratio (INR) was 5.91. N-acetylcysteine (NAC) was briefly started at the OSH, but discontinued due to insufficient evidence in the setting of presumed amatoxin poisoning. On admission to our institution, he was awake and oriented, with normal vital signs. He denied any abdominal pain, nausea, vomiting, or confusion. Ultrasound and MRI of the abdomen did not show evidence of intra- or extrahepatic biliary dilatation. He took no chronic medication, including acetaminophen. Alcohol and drug screen was negative. Hepatitis panel showed a Hepatitis B DNA viral load of 3100 IU/mL; reactive Hepatitis B surface antigen and Be antibody; and non-reactive Hepatitis Be antigen. Although it was unlikely that Hepatitis B was a contributing factor to the liver failure given the low viral load, he was started on tenofovir disoproxil on day 7 after ingestion. Based on his ingestion of home-grown mushrooms prior to symptom onset, amatoxin poisoning from *Amanita phalloides* was highest on the differential diagnosis.

The patient was medically managed in the medical intensive care unit with NIH clinical trial protocol NCT00915681. He was made nil per os (NPO) and treated with IV fluids (received 3 liters of IV fluid boluses, followed by maintainence IV fluids at 200-300 mL/hour) for goal urine output of 2-3ml/kg/hr; and IV octreotide (200mcg bolus followed by 50 mcg/hr continuous infusion) to decrease gallbladder contraction and prevent further excretion of amatoxin from the gallbladder. On Day 5 after ingestion, he was started on IV milk thistle extract (Silibinin-Legalon), which is currently available through request from the primary investigator of clinical study NCT00915681, to inhibit amatoxin uptake and enhance its excretion into the bile. On day 6 after ingestion, there was an improvement in his transaminases (AST decreased to 401U/L and ALT decreased to 2645 U/L) and synthetic function (INR decreased to 3.29), but the ALP was stable at 115 U/L, and there was worsening of his indirect hyperbilirubinemia (Tbili increased to 15.1 mg/dL). Per trial protocol, 30 hours after the initiation of IV silibinin, the patient was initiated on a regular diet and octreotide was stopped. On day 10 after ingestion, the IV silibinin was completed, and his liver function panel was markedly improved (AST was 71 U/L, ALT 866 U/L, ALP 146 U/L, INR 2.02) with the exception of a persistent direct hyperbilirubinemia (Tbili 17.6 mg/dL, dBili 14.0 mg/dL). On day 11 after ingestion, the patient continued to exhibit no signs of altered mental status, so was discharged home. Three weeks after discharge, follow-up labs revealed normalization of his transaminases (AST 40 U/L, ALT 31 U/L) and synthetic function (INR 1.3) concurrent with improvement of his hyperbilirubinemia (Tbili 2.2 mg/dL, dBili 1.3 mg/dL).

DISCUSSION

Amatoxin poisoning is a rare yet serious cause of liver injury. In one case review, up to 30% of patients had a fatal intoxication.[1] Native to Europe, the *Amanita phalloides* mushroom is now commonly seen in North America, typically in coastal California, with increasing reports of intoxication on the East Coast.[1] Colloquially known as the 'Death Cap', this mushroom has a white to yellowish-green cap (pileus), free gills (lamellae), a stem that often has a ring below the cap, and a bulbous base encapsulated by the volva. Its innocuous appearance, along with its

similarity to the edible Volvariella volvacea species poses a difficult challenge for mushroom foragers.

The mushroom's toxicity lies within the phallotoxins and amatoxins within the mushroom. Phallotoxins damage cellular membranes of enterocytes, thus inducing gastrointestinal (GI) symptoms including nausea, vomiting, and severe diarrhea beginning 6-24 hours after ingestion. Amatoxins, specifically the thermostable α-amanitin peptide, has been shown to be the main agent of hepatotoxicity with lethal doses as low as 0.1 mg/kg body weight. Once absorbed through the GI tract, α-amanitin is transported to the liver and concentrated into the hepatocytes by membrane transport proteins. α-amanitin then binds directly to ribonucleic acid (RNA) polymerase II, thereby inhibiting transcription and downstream protein synthesis, and ultimately leading to cell death and hepatic centrilobular necrosis.[1]

Management of patients presenting with acute liver failure secondary to amatoxin poisoning can range from supportive measures to liver transplantation, depending on clinical severity. There is not a current randomized clinical trial in the United States to guide management, and there is currently no antidote for amatoxins. However, over the past several decades, research efforts have been made to identify methods to decrease uptake of the toxin into hepatocytes. Two such treatments are penicillin G and silibinin dihemisuccinate, a constituent of the Mediterranean milk thistle. Both are inhibitors of the organic anion transport polypeptide 1B3 membrane transporters, which are responsible for the uptake of amatoxins into hepatocytes.[1, 2] Retrospective studies have illustrated improved mortality among patients treated with IV silibinin, but there is indeterminate clinical efficacy among patients treated with antibiotics (penicillin G, ceftazidime) and antioxidants (vitamin C, cimetidine).[1, 2]

In our patient, NAC therapy was initiated within 24 hours of toxin ingestion, followed by silibinin infusion on day 5 after ingestion. With appropriate fluid resuscitation, high urinary output, and rapid escalation of care to the ICU per treatment protocol outlined in the NIH clinical trial (NCT00915681)[1], our patient improved clinically and did not require liver transplantation. Although the patient had active hepatitis B infection, his liver function tests had significantly improved on the amatoxin treatment protocol prior to the initiation of antiviral therapy.

KEY POINTS

- *Amanita phalloides* poisoning puts patients at risk for developing acute liver failure that may require liver transplantation
- Clinical trials show that IV silibinin may have a role in preventing acute liver failure.

REFERENCES

1. Escudie L, Francoz C, Vinel J, et al. Amanita phalloides poisoning: Reassessment of prognostic factors and indications for emergency liver transplantation. Journal of Hepatology 2007: 46:466-473.
2. Wolfe BE, Richard F, Cross HB, et al. Distribution and abundance of the introduced ectomycorrhizal fungus Amanita phalloides in North America. New Phytol 2010;185:803–816.
3. Santi L, Maggioli C, Mastroroberto M, Tufoni M, Napoli L, and Caraceni P. "Acute Liver Failure Caused by Amanita phalloides Poisoning," International Journal of Hepatology, vol. 2012, Article ID 487480, 6 pages, 2012.
4. Letschert K, Faulstich H, Keller D, Keppler D. Molecular characterization and inhibition of amanitin uptake into human hepatocytes. Toxicol Sci 2006;91(1):140.
5. F. Enjalbert, S. Rapior, J. Nouguier-Soulé, S. Guillon, N. Amouroux, and C. Cabot, "Treatment of amatoxin poisoning: 20-Year retrospective analysis," Journal of Toxicology, vol. 40, no. 6, pp. 715–757, 2002.
6. Jeanine Ward, Kishan Kapadia, Eric Brush, Steven D. Salhanick, Amatoxin Poisoning: Case Reports and Review of Current Therapies, The Journal of Emergency Medicine, Volume 44, Issue 1, January 2013, Pages 116-121, ISSN 0736-4679.
7. Mitchell, ST. New Comprehensive Amatoxin Mushroom Poisoning (AMP) Treatment Protocol. Clin Tox. 2010;48:628.