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Acute Liver Injury Due to Amanita Phalloides Toxicity in The National Capital Region of the United States

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1. Abstract

Amatoxin poisoning is considered a life-threatening medical emergency beginning with delayed onset of gastrointestinal symptoms followed by acute liver injury that may progress to acute liver failure requiring a liver transplantation. Here we report a case of a 69-year-old male who initially presented with nausea and watery diarrhea after previous ingestion of wild mushrooms. He was transferred to our liver transplant center in the National Capital Region of the United States for further management of his acute liver injury. The mushroom specimens were analyzed by a local mycologist and confirmed to be consistent with the Amanita phalloides species. The patient was successfully treated with n-acetylcysteine and silibinin infusions avoiding the need for liver transplantation. His course was complicated by acute renal failure requiring the initiation of intermittent hemodialysis and a rare pancolitis thought to be secondary to amatoxin.

2. Introduction

Poisonous Amanita mushrooms grow in moist, shaded, leafy areas under hardwood trees in various regions across the globe [1]. Cases of mushroom poisoning due to amatoxin are rare but have been increasing as mushroom foraging has gained in popularity for their editability or hallucinogenic properties [1]. Amatoxin is produced by several mushroom species with the most fatalities attributed to Amanita phalloides [1]. Amatoxin poisoning is considered a life-threatening medical emergency beginning with delayed onset of gastrointestinal symptoms followed by acute liver injury that may progress to acute liver failure requiring a liver transplant [1]. A variety of treatment strategies have been utilized including supportive care, gastrointestinal decontamination, amatoxin inhibitors and antioxidants but the establishment of a standardized protocol has been limited by the lack of randomized controlled trials [1]. Therefore, increasing awareness and establishing an early diagnosis of amatoxin poisoning is critical to reducing the number of fatalities. In this study, we report a case of acute liver injury due to Amanita phalloides toxicity complicated by pancolitis and acute renal failure in the National Capital Region of the United States (US).

3. Clinical Summary

A 69-year-old male with a history of non-insulin dependent type 2 diabetes mellitus presented to a liver transplant center in the National Capital Region of the US as a transfer for acute liver injury and acute kidney injury after wild mushroom ingestion. The patient reported that he went foraging for button cap mushrooms in a nearby wooded area and consumed what he had collected the following day at home. Four days after ingesting the mushrooms, he presented to a local hospital with one day of nausea and watery diarrhea. The initial laboratory results reported at that hospital were as follows: ALT 3,269, AST 1,679, internationalized ratio (INR) 1.2, total bilirubin 1.7, alkaline phosphatase 69, blood urea nitrogen (BUN) 100, creatinine 9.28, sodium 128, potassium 6.7, and blood glucose 509. He initially received one dose of penicillin G 2 million units intravenous (IV), albuterol, insulin, ondansetron, and intravenous fluids (IVF). The pa-

tient was transferred the following day to the liver transplant center in the National Capital Region to initiate n-acetylcysteine (NAC) and silibinin infusions for the treatment of a presumed amatoxin poisoning in accordance with the National Capital Poison Center (NCPC) recommendations. An Investigational New Drug (IND) application was submitted and approved by the Food and Drug Association (FDA) under the expanded access program for the use of silibinin in this patient's case. On arrival to the liver transplant center, the patient's vitals were within normal limits. On exam, there was no altered mental status, asterixis, scleral icterus or jaundice. The patient received a loading dose of silibinin IV 5 mg/kg over 1 hour and then was continued on 20 mg/kg/day. He was also started on NAC IV 150mg/kg for 1 hour, 50mg/kg for 4 hours and then was continued on 100 mg/kg for 16 hours. He received a second dose of penicillin G 2 million units IV and continued to receive IVF. The mushrooms were obtained from the patient's belongings and sent to the NCPC for identification by a local mycologist (Figure 1). The next day, 6 days post-ingestion, the patient's aminotransferase levels peaked at ALT 7,115 and AST 3,644 (Figure 2). The patient's mental status was still intact, and his INR remained less than 2. He was continued on the NAC and silibinin IV infusions. According to the NCPC, the mycologist confirmed that the mushrooms were consistent with the Amanita phalloides species. The patient then completed a total of 4-days of silibinin and NAC IV infusions. On the day of discharge, 23 days post-ingestion and 15 days after completion of silibinin and NAC IV infusions, the patient had an ALT 19, AST 27, and INR 1.2. The patient's course was complicated by bloody bowel movements as many as 10 per day beginning 7 days post-ingestion. An infectious workup was performed and negative including Clostridium difficile polymerase chain reaction, Giardia IgA, stool ova and parasites and stool bacterial cultures. A computed tomography (CT) scan of the abdomen and pelvis without IV contrast was performed and showed pancolonic wall thickening most pronounced in the ascending and proximal transverse colon, compatible with colitis (Figure 3). His hemoglobin slowly down trended down from 15.9 to 8.2 but then stabilized and he did not require any transfusions. After several days of supportive care, the patient's bloody bowel movements had resolved. Additionally, the patient had presented with an acute kidney injury without immediate requirements for dialysis. Over the course of his hospital stay, his creatinine continued to increase reaching 13.14 with a BUN remaining over 100 as well as persistent electrolyte abnormalities. For this reason, the patient was placed on intermittent hemodialysis (iHD) and arrangements were made for the patient to continue iHD at an outpatient center upon hospital discharge.

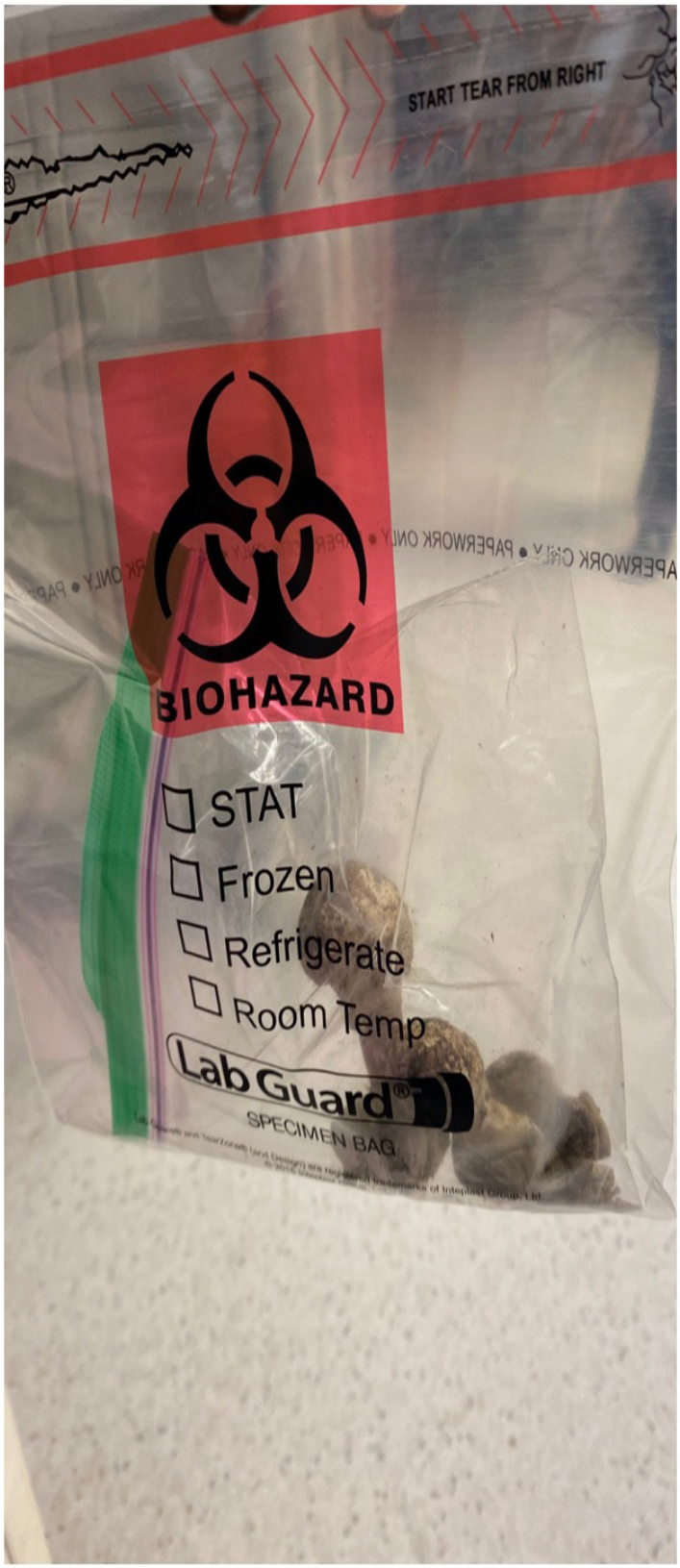

Figure 1. Photograph taken of the mushroom specimens that were obtained from the patient and sent to the National Capital Poison Center.

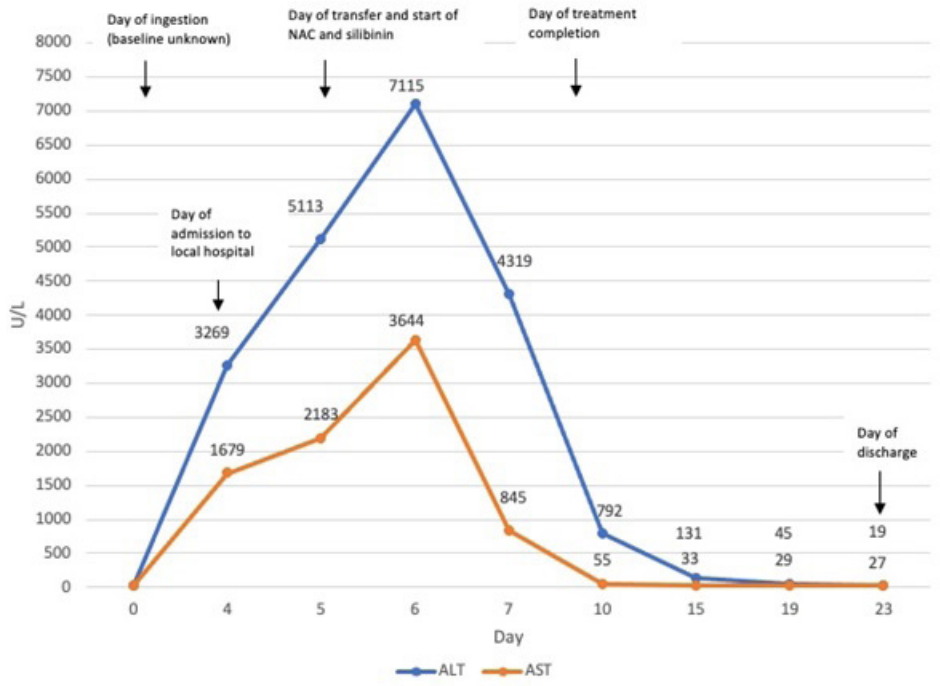

Figure 2. Trend in aminotransferase levels after ingestion of wild mushrooms. Day 0 represents day of ingestion. The patient's aminotransferase levels on day 0 were unknown.

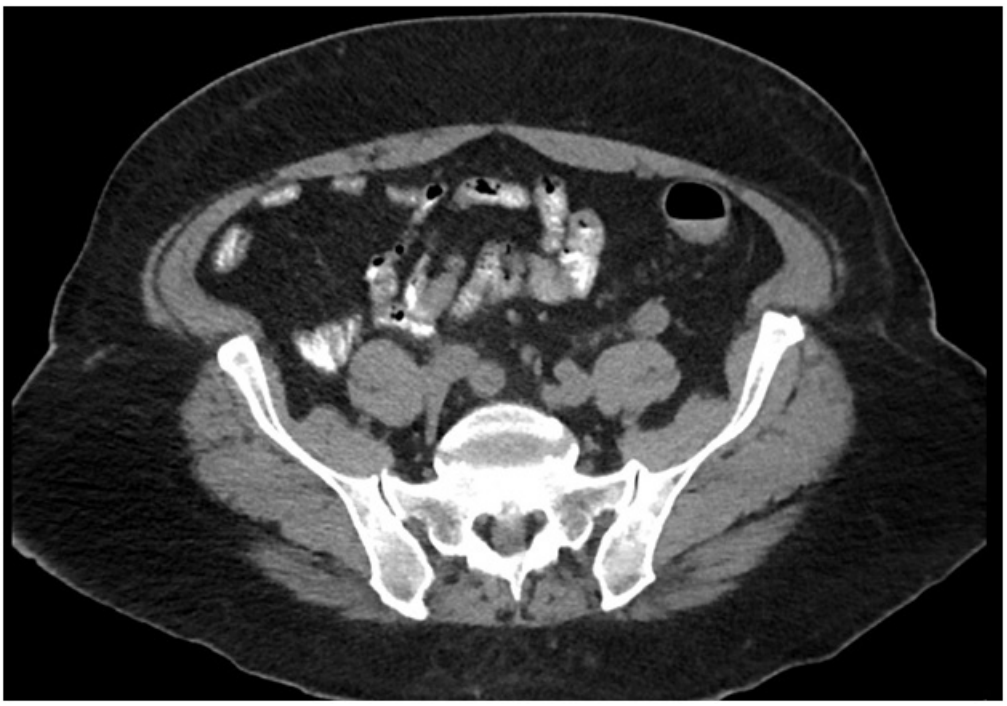

Figure 3. Computed tomography scan of the abdomen and pelvis without IV contrast showing pancolonic wall thickening most pronounced in the ascending and proximal transverse colon, compatible with colitis.

4. Discussion

As the popularity of wild mushroom forging has grown in the US, there has been a rise in mushroom poisonings observed over the recent years. One study analyzed 6,600 cases of mushroom toxicity reported to the National Poison Control Data System in 2012 and found 44 cases to be associated with amatoxin poisoning some of which were fatal [1]. In 2016, there was an outbreak of 14 cases reported to the California Poison Control Center in which all but one experienced hepatoxicity and 3 required liver transplantation [2]. To our knowledge and discussion with the NCPC, there have been no known confirmed cases of Amanita phalloides mushroom toxicity reported in the recent years within the National Capital Region. This case calls for physicians practicing in this area of the country to include amatoxin poisoning on their differential for acute liver injury. The symptoms of amatoxin poisoning often begin with a latency period of 6-40 hours after ingestion, followed by the onset of profuse watery diarrhea lasting 12-24 hours that typically results in severe volume depletion and may also contain blood. Then, there is a clinically silent phase that develops as symptoms resolve but this eventually progresses to deterioration of liver and kidney function [3]. Our patient's presentation was consistent with this description; however, his gastrointestinal symptoms were delayed approximately 72 hours from ingestion. Furthermore, after aminotransferase levels peaked, his diarrhea evolved into multiple bloody bowel movement lasting for several days. The pancolitis observed on CT imaging of the abdomen was attributed to the amatoxins after other causes such as infection had been ruled out. His course was also further complicated by acute renal failure leading to the initiation of hemodialysis. Amatoxin is known to interfere with protein synthesis affecting cells with high metabolic rates such as hepatocytes, gastrointestinal and renal tubular cells, which aligns with the clinical manifestations seen in this case [3]. Although acute kidney injury and renal failure are more common manifestations, there are few documented cases of colitis resulting from amatoxin poisoning. One report from 2015 described a patient with severe amanita poisoning who developed an ulcerating ileocolitis, which was observed on CT scan and confirmed with biopsy. They noted the patient had ingested a large quantity of Amanita phalloides and speculated that there may be an association between the amount consumed and damage to the bowel [4]. Diagnosis of acute liver injury due to amatoxin poisoning relies heavily upon the patient's clinical presentation along with confirmatory analysis of the species of mushroom due to the lack of widely available testing [3]. In this case, a urine sample was obtained on admission to send for amatoxin enzyme linked immunosorbent assay testing; however, the hospital laboratory including send out facilities were not capable of performing this test. The National Medical Service Laboratory recommended by the NCPC was contacted but they had reported that this type of testing was no longer available. Given the patient presented to the liver transplant center 5-days after ingestion, the clinical utility of this test would have been low regardless as the analysis is only highly sensitive within 48 hours of ingestion [3]. The limited availability of testing and short window of utility emphasizes the importance of early identification of the specimens. Fortunately, in this case, the mushrooms were collected from the patient and sent to a local mycologist by the NCPC who confirmed the specimens were consistent with the Amanita phalloides species. For the treatment of his amatoxin poisoning, this patient received IV silibinin, NAC and penicillin G along with supportive care including intravenous fluid resuscitation. These are among the most common therapies utilized in the management of amanita toxicity based on published case reports; however, there is currently no standardized treatment protocol due to a lack of large randomized clinical trials to support their efficacy [1]. The patient in this case completed a 4-day continuous IV infusion of silbinin. An IND application was submitted and approved by the FDA under the expanded access program for the use of silibinin in this patient's case. Silibinin competes with amatoxin for transmembrane transport into hepatocytes and disrupts enterohepatic circulation thus having a protective effect on hepatocytes. It is recommended to be used within 48 hours of ingestion and continued for 2-4 days [3]. In this case, the patient presented 4 days after ingestion and was started on silibinin upon arrival to the liver transplant center 5 days post-ingestion. The patient's improvement and normalization of aminotransferase levels and lack of progression to acute liver failure requiring transplantation suggests that silibinin may be efficacious outside of this 48-hour window and warrants further investigation. The patient also received NAC, which was discontinued after 4 days once the patient's ALT dropped below 1,000. NAC is well known for its antioxidant properties and most often used in acute liver injury in cases of toxic exposures [3]. A 2002 retrospective study that analyzed 2,108 hospitalized patients with amatoxin poisoning found that patients treated with NAC had the most positive effects with a 94% survival rate in those also receiving silibinin [5]. The patient additionally received two doses of IV penicillin G in accordance with the NCPC recommendations. However, this therapy was discontinued upon further evaluation by the liver transplant team. Penicillin G has been used in many cases of Amanita poisoning to promote excretion of the toxin by preventing it from binding to plasma proteins [3]. A study from 2008 conducted a review of existing case reports and found that silibinin monotherapy had a lower combined mortality and transplant rate than in combination penicillin G [5]. Therefore, penicillin G was not continued in this patient's case once he had begun treatment with silibinin. In conclusion, this case demonstrates successful treatment of acute liver injury secondary to amatoxin poisoning, which was complicated by the rare development of pancolitis. The patient avoided progression to acute liver failure requiring transplantation after receiving a 4-day treatment course with silibinin and NAC IV infusions. The initiation of silibinin was 5 days following mushroom ingestion, which indicates that there may be a therapeutic benefit outside of the current recommended window of starting within 48-hours post-ingestion.

Given the barriers to early diagnosis and treatment such as the delayed onset of symptoms and limited availability of amatoxin testing and lack of randomized controlled trials, it is critical that successful treatment outcomes as in this case be disseminated amongst clinicians to help guide them in the management of acute liver injury. Overall awareness of the presence of Amanita phalloides and other amatoxin producing species is required to discourage mushroom foraging in regions with known cases of toxicity such as this one in the National Capital Region of the US.

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