Hepatotoxicity from ingestion of wild mushrooms of the genus *Amanita* section *Phalloideae* collected in Mexico City: two case reports

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ABSTRACT

We present two cases of acute liver injury resulting from consumption of wild mushrooms. The first case was a male who developed acute hepatitis after ingestion of diverse mushrooms including *Amanita* species. His clinical course was favorable with complete recovery of liver function. The second case was a male who developed acute liver failure (ALF) after ingestion of *Amanita bisporigera*. He required MARS therapy as a bridge to liver transplantation but transplantation was not performed because he succumbed to multiorgan failure. There are few trials demonstrating the efficacy of the different treatments for mushroom poisoning. These cases demonstrate that the consumption of wild mushrooms without proper knowledge of toxic species represents a serious and under recognized health problem.


INTRODUCTION

Ingestion of toxic macroscopic mushrooms (mycetism) occurs infrequently but can be a medical urgency. Patients arrive to the Emergency Department and show diverse symptoms, many of which overlap with gastroenteritis or other benign clinical syndromes. Clinicians must have a high index of suspicion for mushroom toxicity in any patient reporting recent wild mushroom ingestion with a concomitant toxic syndrome. Most lethal exposures (90%) occurring in Europe and North America are attributed to *Amanita phalloides* and *A. virosa*; however, in Mexico other species such as *Amanita arocheae*, *A. bisporigera*, *A. verna* and *A. virosa* under the same section (*Phalloideae*) are equally toxic. Fourteen distinct types of mushroom poisoning have been described. *Amanita* species toxicity is characterized by its late onset, occurring between 6 and 24 h or more post-ingestion. We present two cases of hepatotoxicity resulting from ingestion of wild mushrooms gathered in the metropolitan area of Mexico City. Both patients were managed in a tertiary care center yet had dramatically different clinical outcomes.

CASE REPORT

Case 1

A 62-year-old man was referred from a secondary care hospital with jaundice and a recent history of eating wild mushrooms collected in Talpan Park in Mexico City. He presented to the emergency room twelve hours after mushroom ingestion with
crampy, epigastric pain of moderate intensity, nausea and loose stools. The patient was hydrated and received antiemetics and analgesics for the first 24 h. On the third day after ingestion, he developed jaundice and dark urine and was referred to our tertiary care center for abnormal liver biochemistry tests. His past medical history was remarkable only for irritable bowel syndrome treated with tegaserod 6 mg twice a day for three months and alcohol intake less than 30 g every 4 months. At admission his vital signs were normal. His physical exam revealed scleral icterus, jaundice, mild abdominal tenderness, and normal mental status. Laboratory tests were remarkable for elevated ALT > 3,900 U/L, total bilirubin > 20 mg/dL and prolonged PT 40/12 s (Table 1). Serological markers for hepatitis A, B and C were negative. He was given intravenous hydration, ceftazidime, and ursodeoxycholic acid. Within 36 h he showed clinical improvement. He never experienced encephalopathy or serious coagulopathy.

Samples of remnants of the wild mushrooms collected by the patient were evaluated in the Mycology Area of the Department of Comparative Biology of the Faculty of Sciences of Mexico’s National Autonomous University (UNAM). The species identified were Amanita bisporigera, A cf. verna (section phalloideae) A. flavorubens (section Validae) and Russula sp. Some samples were in process of decomposition (Table 2, Figure 1).

Of note, the patient’s wife also ate a portion of the wild mushrooms and developed diarrhea with electrolyte abnormalities but no hepatotoxicity. Details of the proportion of each species and quantity of mushrooms consumed by the patient and his wife were not known.

**Case 2**

A 47-year-old male agricultural worker was referred from a secondary care hospital for acute hepatitis after ingestion of wild mushrooms collected in a

**Table 1. Evolution of laboratory test (case 1).**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>09/03/07</th>
<th>09/05/07</th>
<th>09/07/07</th>
<th>09/10/07</th>
<th>10/12/07</th>
<th>11/19/08</th>
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<td>Glucose mg/dL</td>
<td>109</td>
<td>128</td>
<td>95</td>
<td>89</td>
<td>99</td>
<td>-</td>
</tr>
<tr>
<td>Creatinine mg/dL</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>1.0</td>
<td>0.9</td>
<td>-</td>
</tr>
<tr>
<td>TB mg/dL</td>
<td>8.6</td>
<td>12.7</td>
<td>13.83</td>
<td>20.58</td>
<td>1.98</td>
<td>0.71</td>
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<tr>
<td>DB mg/dL</td>
<td>3.9</td>
<td>9.31</td>
<td>9.21</td>
<td>14.11</td>
<td>1.08</td>
<td>0.12</td>
</tr>
<tr>
<td>Albumin g/L</td>
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<td>3.4</td>
<td>3.3</td>
<td>3.3</td>
<td>3.8</td>
<td>4.2</td>
</tr>
<tr>
<td>ALT U/L</td>
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<td>3,943</td>
<td>3587</td>
<td>688</td>
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<td>22</td>
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<tr>
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<td>626</td>
<td>435</td>
<td>132</td>
<td>40</td>
<td>21</td>
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<tr>
<td>ALP U/L</td>
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<td>175</td>
<td>170</td>
<td>291</td>
<td>273</td>
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<tr>
<td>GGT U/L</td>
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<td>89</td>
<td>89</td>
<td>396</td>
<td>139</td>
<td>21</td>
</tr>
<tr>
<td>LDH U/L</td>
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<td>48</td>
<td>510</td>
<td>440</td>
<td>304</td>
<td>-</td>
</tr>
<tr>
<td>Hb g/dL</td>
<td>15.8</td>
<td>16</td>
<td>16.7</td>
<td>18.1</td>
<td>16.3</td>
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<tr>
<td>WBC (10³/µL)</td>
<td>8,500</td>
<td>8,700</td>
<td>9,100</td>
<td>9,500</td>
<td>8900</td>
<td>-</td>
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<tr>
<td>Platelets (10³/µL)</td>
<td>106,000</td>
<td>118,000</td>
<td>112,000</td>
<td>95,000</td>
<td>142,000</td>
<td>-</td>
</tr>
<tr>
<td>PT (sec)</td>
<td>40/12</td>
<td>33/12</td>
<td>24.9/12.5</td>
<td>15.5/12.6</td>
<td>12.7/12.4</td>
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</table>

Table 2. Identification of wild mushrooms collected (case 1).

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Species identified</th>
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<tbody>
<tr>
<td>Basidiome*</td>
<td>Amanita flavorubens</td>
</tr>
<tr>
<td>Stem</td>
<td>Amanita flavorubens</td>
</tr>
<tr>
<td>Basidiome</td>
<td>Amanita bisporigera (subgenus Lepidella section Phalloideae)</td>
</tr>
<tr>
<td>Pileus</td>
<td>Amanita cf. verna (subgenus Lepidella section Phalloideae)</td>
</tr>
<tr>
<td>Basidiome</td>
<td>Russula sp (impossible to determine species because high degree of decomposition)</td>
</tr>
<tr>
<td>Basidiome</td>
<td>Amanita cf. verna</td>
</tr>
</tbody>
</table>

*Basidiome (fruiting body), is a multicellular structure on which spore-producing structures are borne.
Table 3. Evolution of laboratory test (case 2).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>09/15/10</th>
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<th>09/17/10</th>
<th>09/18/10</th>
<th>09/19/10</th>
<th>09/20/10</th>
<th>09/21/10</th>
<th>09/22/10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets*</td>
<td>365</td>
<td>231</td>
<td>156</td>
<td>92</td>
<td>62</td>
<td>55</td>
<td>75</td>
<td>52</td>
</tr>
<tr>
<td>Glucose</td>
<td>105</td>
<td>54</td>
<td>137</td>
<td>65</td>
<td>189</td>
<td>133</td>
<td>176</td>
<td>125</td>
</tr>
<tr>
<td>Urea (mg/dL)</td>
<td>137</td>
<td>87</td>
<td>65</td>
<td>33</td>
<td>37</td>
<td>55</td>
<td>91</td>
<td>100</td>
</tr>
<tr>
<td>Creatinine</td>
<td>5.3</td>
<td>2.2</td>
<td>1.55</td>
<td>1.22</td>
<td>1.86</td>
<td>3</td>
<td>4.5</td>
<td>4.26</td>
</tr>
<tr>
<td>TB (mg/dL)</td>
<td>3.52</td>
<td>7.36</td>
<td>7.19</td>
<td>9.74</td>
<td>12.37</td>
<td>11.2</td>
<td>15</td>
<td>14.7</td>
</tr>
<tr>
<td>DB (mg/dL)</td>
<td>3.02</td>
<td>6.52</td>
<td>6.25</td>
<td>7.2</td>
<td>8.18</td>
<td>8.68</td>
<td>11.33</td>
<td>9.42</td>
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<tr>
<td>ALT (U/L)</td>
<td>1,377</td>
<td>2,194</td>
<td>2,675</td>
<td>3,146</td>
<td>1,814</td>
<td>794</td>
<td>511</td>
<td>306</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>1,358</td>
<td>1,663</td>
<td>2,215</td>
<td>2,064</td>
<td>552</td>
<td>114</td>
<td>60</td>
<td>44</td>
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<tr>
<td>GGT (U/L)</td>
<td>-</td>
<td>74</td>
<td>58</td>
<td>69</td>
<td>60</td>
<td>47</td>
<td>53</td>
<td>47</td>
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<tr>
<td>LDH (U/L)</td>
<td>2,080</td>
<td>2,934</td>
<td>3,406</td>
<td>2,239</td>
<td>911</td>
<td>526</td>
<td>649</td>
<td>779</td>
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<tr>
<td>ALP (U/L)</td>
<td>-</td>
<td>104</td>
<td>98</td>
<td>132</td>
<td>139</td>
<td>89</td>
<td>99</td>
<td>101</td>
</tr>
<tr>
<td>Albumin</td>
<td>-</td>
<td>3.34</td>
<td>3.04</td>
<td>3.2</td>
<td>3.11</td>
<td>2.3</td>
<td>2.36</td>
<td>2.6</td>
</tr>
<tr>
<td>PT (s)</td>
<td>58 /13</td>
<td>76.3/12</td>
<td>75.9/12</td>
<td>58.8</td>
<td>50.3</td>
<td>46.4</td>
<td>60.3</td>
<td>40.9/13</td>
</tr>
</tbody>
</table>

* WBC and platelets reported as (10^3)/μL; glucose and creatinine reported in mg/dL, albumin reported in g/L. TB: Total bilirubin. DB: Direct bilirubin. ALT: Alanine aminotransferase. AST: Aspartate aminotransferase. PT: Prothrombin time. GGT: Gamma glutamyl transferase. LDH: Lactic dehydrogenase. ALP: Alkaline phosphatase. WBC: White blood cell. Alb: Albumin.

wooden area next to his home in southern Mexico City. Ten hours after ingestion, he developed severe, crampy mesogastric pain that radiated to the lower back, accompanied by nausea, frequent vomiting, and more than 10 watery bowel movements without mucus, blood or fever. He was initially given intravenous hydration, antiemetics, analgesics, loperamide and trimethoprim-sulfamethoxazole. After 24 h
the patient developed kidney and liver dysfunction and was referred to our tertiary care hospital. His medical history was remarkable only for occasional use of diclofenac for knee joint pain. At admission his blood pressure was 100/60, heart rate 90 beats/min, respiratory rate 20 breaths/min, and he was afebrile. He had scleral icterus, right upper quadrant pain, and a normal neurologic exam without hepatic encephalopathy. Blood work demonstrated acute renal failure, metabolic acidosis, hypoglycemia, prolonged PT and significant abnormalities in the liver biochemistries. Abdominal ultrasound revealed no significant changes in liver or biliary tract. He was admitted to the Intensive Care Unit with an Apache II score of 10 points (Table 3).

Silymarin 420 mg (Legalon®, Nycomed SA, Mexico City) therapy was administered every 8 h. On the fifth day following the ingestion, the patient developed acute pancreatitis with a serum amylase of 455 U/L and lipase of 1418 U/L. Subsequently, hepatic encephalopathy appeared and rapidly progressed to grade IV requiring intubation, norepinephrine infusion, sedation and lactulose. He was evaluated as a potential transplant recipient for acute liver failure (ALF). On the sixth day post-ingestion, therapy with Molecular Adsorbent Recirculating System (MARS® Treatment Kit, PrisMARS, Gambro Rostock GmbH, Friedrich-Barnewitz ST3, Rostock, Germany) was initiated in two sessions (12 and 21 h) as a bridge to transplant. The patient’s condition evolved with Glasgow scale of 6, brain CT showing mild swelling, rapid progression of liver and renal failure, and shock refractory to treatment. He died on the tenth day post-ingestion. Liver biopsy was performed post-mortem and showed multiacinar necrosis, bridging necrosis, canaliculcholestasis with neoformation of bile ducts and macrovesicular steatosis (Figure 2).

An immature specimen of the wild mushroom collected was also evaluated in the Mycology Area, UNAM. Because the specimen had not yet developed all its morphological characteristics, it could identified only as Amanita aff. bisporigera. In this case, the patient’s wife also ate a small portion of the mushroom and experienced only gastrointestinal upset without liver or kidney injury.

**DISCUSSION**

We present two cases of mushroom-induced hepatotoxicity with distinct clinical courses. The first was an acute toxic hepatitis caused by consumption of Amanita species, with decreased albumin and prolongation of PT but without complications such as hemorrhagic diathesis or encephalopathy. The second case died of multi-organ failure due to ALF despite MARS therapy initiated as a bridge to liver transplantation. Although the albumin dialysis therapy appeared to result in an initial improvement, its utility was likely limited because of the delay in initiation.

In the first case of mycetism, the only edible species were Rusulla sp; the other species such as Amanita flavorubens (section Validae) may result in abdominal pain and toxicity when eaten raw. Unfortunately, the distinction between edible and toxic mushrooms is based on detailed knowledge of their morphological characteristics. There is no practical, simple method that could allow most individuals to make this distinction. For example, while different species of edible mushrooms are white like the typi-
cal white button mushroom (Agaricus spp, Amanita
tuza, etc.) or yellow (Amanita caesarea, A. yema, A.
tullossi, or A. flavorubens), most toxic species in
North America are also white.

Nearly 74,000 species of mushrooms in the world
have been identified,6 of which three main families
contain lethal amatoxins:

• Amanitaceae. Within genus Amanita, including
most of the 44 species described for the section
phalloideae.

• Cortinariaceae. Of the genus Galerina includ-
ing species such as G. autumnalis, G. badius, G.
marginata, G. sulciceps, G unicolor, G.venenata.

• Agaricaceae. Including Chlorophyllum molybi-
des and species of the genus Lepiota, among the
most notable L. Helveola, L. brunneoincarnata,
L. sunincarnata.5,7

Toxins of the genus Amanita are classified into
three groups: amatoxins, phallotoxins and viro-
toxins. The virotoxins and phallotoxins act quickly,
typically in 1-2 h. The phallotoxins are poorly
absorbed and are responsible for the gastrointesti-
nal symptoms. Amatoxins (cyclo-octapeptides) have
a slower onset, typically 10 to 15 h post-ingestion,
but are 10 to 20 times more toxic. Amatoxins are
resistant to heat and freezing, and cannot be dena-
tured by cooking or digestive enzymes.8-10

The lethal dose of amatoxins is < 0.1 mg/kg of
body weight and a mature mushroom can contain a
fatal dose of 8-12 mg. The amatoxins are mainly pre-
sent in the pileus, ring and stem of the basidiome
(or fruiting body, on which spore-producing struc-
tures are borne). The severity of poisoning depends
on the amount of mushroom ingested.11-13 The ama-
toxins inhibit protein synthesis in enterocytes, hepa-
tocytes and renal proximal tubular cells. Hepatocellular damage is due to the recapture of
amatoxins, mediated by the organic anion polypepti-
de transporter located in the cytoplasmatic mem-
brane. This polypeptide binds to the subunit of RNA
polymerase II transcription, interfering with DNA,
suppressing the production of RNA, blocking pro-
tein synthesis, and causing cell death.1,9,14,15

Amanita poisoning presents with different clinical
stages:

• The incubation stage, which is an asymptomatic
period between 6 and 12 h after ingestion.

• The gastrointestinal stage characterized by abdo-

• The cytotoxic stage which typically consists of an
apparent clinical improvement after 24 to 48 h fol-
lowed by a progressive deterioration in renal or
liver function.4,14,16

The fourth phase may begin abruptly with coagu-
lopapthy, hepatic encephalopathy, hypoglycemia, and
development of fulminant hepatic failure combined
with acute renal failure.9,17,18 The diagnosis can be
confirmed by the detecting the presence of alpha ama-
nitin in urine. Different methods of analysis (RIA-ra-
dioimmunoassay, HPLC-High Performance Liquid
Chromatographic method, ELISA) are highly sensiti-
ve for detecting alpha amanitin in blood or urine if
they are performed within 48 h prior to ingestion.
However, these tests are not accessible at all sites
and are not routinely performed.19 Mortality from
mushroom poisoning has been found to be as high as
20% in adults and 50% in children. Without trans-
plantation, the probability of surviving due to mush-
room poisoning ranges between 10 and 30%.14,16,20

The following risk factors have been found to confer
a higher morality risk: age < 10 years, female gen-
der, short interval between ingestion and onset of
diarrhea (< 8 h), severe coagulopathy, severe hyper-
bilirubinemia, elevated creatinine, and a rapid increa-
se in prothrombin time.21

There is no specific antidote for mushroom poi-
soning. An accurate taxonomic identification of
the mushroom can be useful in determining prog-
nosis. Treatment should begin with vigorous fluid
resuscitation and an attempt to evacuate the GI
tract. Ipecac syrup is effective only in the first
hour after ingestion. Nasogastric lavage followed
by activated charcoal every 2-4 h to reduce ab-
sorption is also recommended. Forced diuresis
with sodium bicarbonate have been used to elimi-
nate the toxin in the first hours.9,17 Nasobiliary
drainage by endoscopic cholangiography (ERCP)
has been used successfully to remove amatoxins
from enterohepatic circulation but is not perfor-
mated routinely.9

Other medications that have been used in mush-
room poisoning include silymarin (Silybum mari-
anum-Milk Thistle), which inhibits the binding of
toxins to hepatocytes, and competes for the trans-
membrane transporter, thereby interrupting entero-
hepatic circulation of the toxin and reducing
oxidative stress.15,22 Silymarin has been used at do-
ses of 20-50 mg/kg/d orally or through its intrave-
nous form silybin (5 mg/kg bolus and 20 mg/kg/24 h
infusion for three days). Silymarin has been used in combination with other agents so its single contribution is unknown. Comparative prospective studies are needed to demonstrate its real benefits. Other drugs that have been used empirically are high-dose penicillin G, ceftazidime, N-acetylcysteine, or cimetidine. Randomized control trials demonstrating the efficacy of these different therapeutic modalities are lacking.

Several extracorporeal detoxification methods such as charcoal hemoperfusion, plasmapheresis, hemodialysis and MARS, have been used in many transplant centers. MARS therapy is a albumin dialysis method which may remove primary and secondary toxins and support the excretory function, thereby maintaining hemodynamic stability and preventing organ failure. MARS is most useful if started before the onset of gastrointestinal symptoms, and can act as a bridge to liver transplantation. On the other hand, MARS therapy is an invasive and expensive modality, and its utility in Amanita intoxication has only been demonstrated in uncontrolled case reports. There are several reports of successful liver transplantation for mushroom poisoning when ALF is identified early with proper consideration of prognostic factors. One year survival of 65% has been reported.

**CONCLUSION**

Although mushroom poisoning occurs infrequently, it must be recognized promptly so as to implement therapies to limit the absorption of lethal toxins within the first critical hours. Patients with evidence of hepatic impairment should be managed aggressively in tertiary hospitals with liver transplant capacity. In Mexico there is a wide variety of mushrooms and an extensive traditional knowledge about edible mushrooms. However, these cases show that the consumption of wild mushrooms without a clear distinction of edible vs. toxic species represents a serious and under recognized health problem.

**ABBREVIATIONS**

- **ALF**: Acute liver failure.
- **MARS**: Molecular adsorbent recirculating system.
- **ALT**: Alanine aminotransferase.
- **AST**: Aspartate aminotransferase.
- **TB**: Total bilirubin.
- **PT**: Prothrombin time.

**ACKNOWLEDGEMENTS AND DISCLOSURES**


**REFERENCES**