Yonsei Medical Journal
Vol. 41, No. 3, pp. 416-421, 2000

Amanita virosa Induced Toxic Hepatitis: Report of Three Cases

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Abstract

We report here three cases of *Amanita virosa* induced toxic hepatitis. Two of the three cases recovered but the other died 10 days after mushroom ingestion. Since the mortality of *Amanita* mushroom induced toxic hepatitis is very high, prompt diagnosis and aggressive therapeutic measures should be initiated as soon as possible. Our cases showed that the initial serum aminotransferase levels might not predict the clinical outcome of the patient, but that the prothrombin time (PT) seemed to be a more useful prognostic marker. Close monitoring of aminotransferase levels and PT as well as appropriate therapy are recommended. All three cases showed signs of proteinuria and we were able to characterize mixed tubular and glomerular type proteinuria at 3 or 4 days after ingestion in two cases. Among the previously reported Korean cases of suspected *Amanita* induced toxic hepatitis, most species could not be identified except for four cases of *Amanita virosa*. No cases of *Amanita phalloides* induced toxic hepatitis have been identified in Korea so far.

Key Words: *Amanita virosa*, mushroom poisoning, toxic hepatitis, tubular proteinuria

INTRODUCTION

Many cases of *Amanita* induced toxic hepatitis have been reported in the United States.[1-5] Most cases are caused by the genus *Amanita*, particularly by *Amanita phalloides*.[2] Among the less than 60 previously reported Korean cases of suspected *Amanita* induced toxic hepatitis, only four cases of *Amanita virosa (A. virosa)* had been identified definitely prior to this study.[6-8] No *A. phalloides* induced toxic hepatitis case has been identified in Korea so far. Our experience with three cases of *A. virosa* induced toxic hepatitis is discussed in this article.

CASE REPORT

Case 1

A 52 year old woman developed vomiting and profuse diarrhea 10 hours after ingesting wild mushrooms in the Samchok valley, in Kangwondo, Korea in August 1999. After symptomatic improvement for a period of 1 day, she redeveloped similar symptoms and was admitted to hospital 68 hours after ingestion of the mushrooms. On physical examination she was observed to be in mild distress and had normal vital signs. The abdomen was soft with mild abdominal tenderness. Bowel sounds were slightly hyperactive.

Laboratory values for her blood, sampled at admission, were as follows: hemoglobin, 16.3 g/dL (normal for females, 12.0-16.0); hematocrit, 48.6 % (normal for females, 37.0-47.0); leukocyte count, 11,970/μL (normal, 4,000-10,800); platelet count, 354,000/μL (normal, 130,000-400,000); glucose, 129 mg/dL (normal, 70-120); blood urea nitrogen (BUN), 22 mg/dL (normal, 9.1-23.3); creatinine, 0.7 mg/dL (normal, 3.5-1.4); total bilirubin, 3.2 mg/dL (normal 0.2-1.3); prothrombin time (PT), 45.0 sec (normal, 12-14); activated partial thromboplastin time (aPTT), 51.7 sec (normal 29-45); factor V, 11.5% (normal, 50-150%); ammonia, 100 μmol/L (normal, 25-51); aspartate aminotransferase (AST), 9,360 IU/L (normal, 13-37), alanine aminotransferase (ALT), 4,790 IU/L (normal, 7-43). She also showed 1+proteinuria and 1+ketonuria by urine dipstick test. High-resolution SDS agarose gel electrophoresis (Sebia™, Issy-les-Moulineaux, France) of a random urine sample 4 days after ingestion of the mushrooms, showed mixed

Received December 24, 1999
Accepted May 3, 2000
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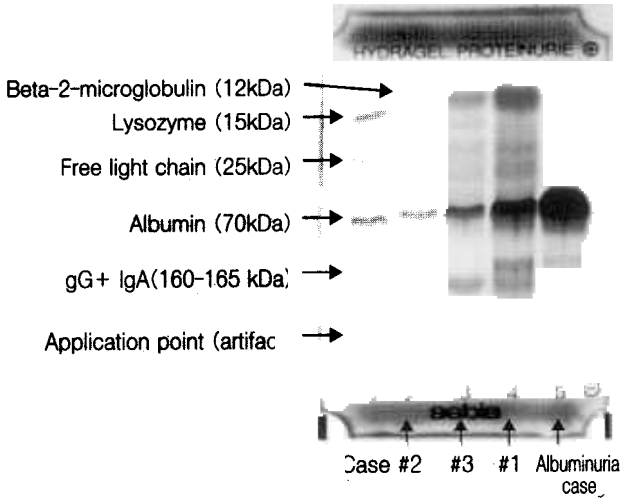

Fig. 1. Characterization of urine protein of the three cases by spot urine SDS agarose gel electrophoresis (Sebia™, France). Lane 1 shows the mixture of standards (lysozyme, free light chain, albumin, and mixture of IgG and IgA). Lane 2 shows the slight albuminuria (1 +) of Case #2 at 3 days after ingestion of A. virosa (Total protein, 42.4 mg/dL; albumin, 7.3 mg/dL). Lane 3 shows the mixed proteinuria (3 +, tubular proteinuria +albuminuria) of Case #3 at 3 days after ingestion of A. virosa (T.protein, 142.6 mg/dL; albumin, 29.1 mg/dL). Lane 4 shows the mixed proteinuria (3 +, tubular proteinuria +albuminuria) of Case #1 at 4 days after ingestion of A. virosa (T.protein, 365.0 mg/dL; albumin, 127.9 mg/dL). Lane 5 shows the glomerular proteinuria (albuminuria) of the nephrotic syndrome case (T.protein, 464 mg/dL; albumin, 450.3 mg/dL) as a control.

(tubular+glomerular) proteinuria as in Lane 4 of Fig. 1. She received a transfusion of fresh frozen plasma to correct coagulopathy and received conservative care including intravenous fluid infusions, electrolyte repletion, and activated charcoal ingestion. She was transferred to the intensive-care unit 4 days after ingestion of the mushrooms due to hepatic encephalopathy. Her aminotransferase level peaked on the fourth day after mushroom ingestion (Fig. 2). Her PT and aPTT improved continuously (Fig. 3). Factor V level increased to 51% and then 64%, on the 6th and 7th days after mushroom ingestion, respectively. She subsequently recovered and was discharged 12 days after the ingestion. PT, aPTT, and serum biochemical parameters of liver function were almost normalized 25 days after ingestion of mushroom (AST, 33 IU/L; ALT 51 IU/L). The mushrooms were identified as *A. virosa* by the examination of spores and by their gross morphology (Fig. 4.).

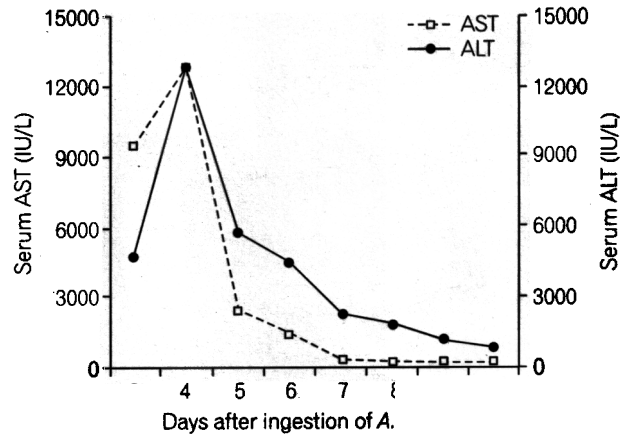

Fig. 2. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) versus days after ingestion of A. virosa in Case 1 (52 year old woman). AST and ALT levels were normalized within 1 month after ingestion.

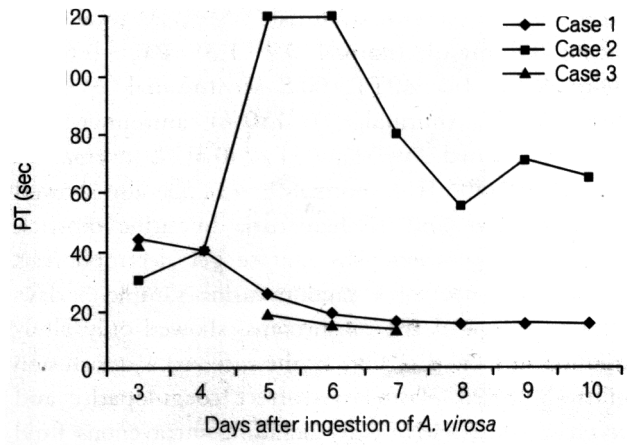

Fig. 3. Prothrombin time (PT) level in the three cases versus days after ingestion of A. virosa. In Case 2, the patient died on day 10 due to fulminant hepatic failure.

Case 2

The 28-year-old daughter of the Case 1 patient developed nausea, vomiting and diarrhea 10 hours after ingesting the mushrooms. After a symptomatic improvement period of 1 day, she developed similar symptoms and was admitted to hospital 68 hours after ingestion of the mushrooms.

Laboratory values for her blood, sampled at admission, were as follows: hemoglobin, 18.3 g/dL (normal for females, 12.0−16.0); hematocrit, 52.4% (normal for females, 37.0−47.0); leukocyte count, 23,890/μL (normal 4,000−10,800); platelet count, 512,000/μL (normal 130,000−400,000); glucose, 182 mg/dL (nor-

Fig. 4. Gross morphology of Amanita virosa.

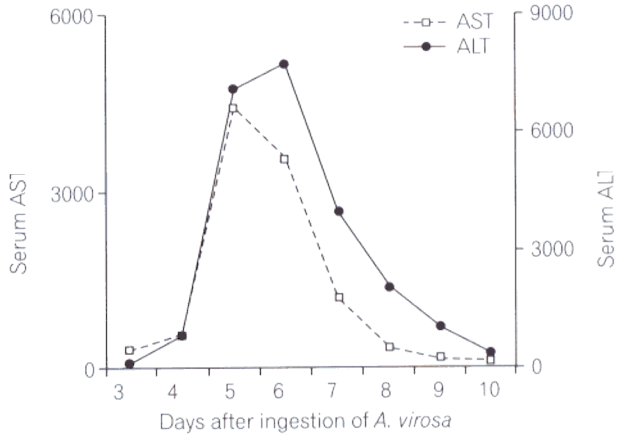

Fig. 5. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) versus days after ingestion of A. virosa in Case 2 (28 year old woman). She died on day 10 due to fulminant hepatic failure.

mal 70−120); BUN, 21 mg/dL (normal 9.1−23.3); creatinine, 1.3 mg/dL (normal 3.5−1.4); total bilirubin, 8.0 mg/dL (normal 0.2−1.3); PT, 30.6 sec (normal 12−14); aPTT, 60.8 sec (normal 29−45); factor V, 6% (normal, 50−150%); ammonia, 146 μmol/L (normal 25−51); AST, 240 IU/L (normal 13−37); ALT, 406 IU/L (normal 7−43). She also showed 2+proteinuria and 1+hematuria by urine dipstick test. High-resolution SDS agarose gel electrophoresis (Sebia™, France) of a random urine sample 3 days after ingestion of the mushrooms, showed only albuminuria in Lane 2 of Fig. 1. She received a transfusion of fresh frozen plasma to correct coagulopathy and received conservative care including intravenous fluid infusions, electrolyte repletion, and activated charcoal ingestion. Her aminotransferase levels were elevated, peaking 6−7 days after mushroom ingestion (Fig. 5). Her PT and PTT became aggravated and the levels were prolonged at the peak at 6−7 days after mushroom ingestion (Fig. 3) and factor V levels were not normalized, 4% and then 12%, 6 and 7 days after mushroom ingestion, respectively. She was transferred to the intensive-care unit 5 days after ingestion of the mushrooms due to hepatic encephalopathy. She developed seizure attacks requiring ventilator care on the sixth day after ingestion. On the next day, the seizure was controlled but acute renal failure developed and she received continuous arterio-venous hemodialysis. She died on day 10 due to fulminant hepatic and multiple organ failure.

Case 3

The 58-year-old male chauffeur of the Case 1 patient developed vomiting and diarrhea 12 hours after ingesting the mushrooms with Case 1 and 2 patients. His symptoms were much improved but he was admitted for possible hepatic failure 80 hours after ingestion of the mushrooms.

Laboratory values for his blood, sampled at admission, were as follows: hemoglobin, 16.2 g/dL (normal 13.0−18.0); hematocrit, 47.5% (normal 38.0−52.0); leukocyte count, 13,320/μL (normal 4,000−10,800); platelet count, 354,000/μL (normal 130,000−400,000); glucose, 161 mg/dL (normal 70−120); BUN, 20 mg/dL (normal 9.1−23.3); creatinine, 1.1 mg/dL (normal 3.5−1.4); total bilirubin, 1.8 mg/dL (normal 0.2−1.3); PT, 43.0 sec (normal 12−14); aPTT, 59.1 sec (normal 29−45); ammonia, 85 μmol/L (normal 25−51); AST, 5,350 IU/L (normal 13−37); ALT, 4,875 IU/L (normal 7−43). He also showed 3+proteinuria and 1+bilirubinuria by urine dipstick test. High-resolution SDS agarose gel electrophoresis (Sebia™, France) of a random urine sample 3 days after ingestion, showed mixed (tubular+glomerular) proteinuria as in lane 3 of Fig. 1. His aminotransferase level peaked 4 days after mushroom ingestion (Fig. 6). He was discharged 6 days after ingestion of the mushrooms. His serum biochemical parameters of liver function were completely normalized 25 days after ingestion (AST, 33 IU/L; ALT, 41 IU/L).

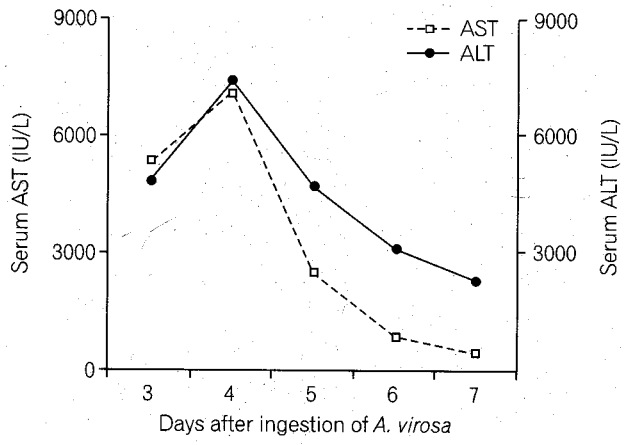

Fig. 6. *Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) versus days after ingestion of A. virosa in Case 3 (58 year old man). AST and ALT levels were normalized within month after ingestion.*

ALT levels were elevated in all three patients and peaked within 48−72 hours after mushroom ingestion in the patients 1 and 3. PT was prolonged in the three patients within 48 hours after ingestion but began to be corrected within 96 hours (Fig. 3).

DISCUSSION

Mushrooms of the genus *Amanita* contain amatoxins, thermostable bicyclic peptide toxins composed of eight amino acids with a molecular mass of about 900 Dalton Amatoxins, especially amanitin, cause cellular injury by inhibiting RNA polymerase.[9-12] The greatest damage is to cells with rapid rates of turnover, such as gastrointestinal mucosa cells, hepatocytes, and renal tubular cells.[11,12] Amatoxins are taken up by hepatocytes, excreted into the bile, and reabsorbed.[13] This enterohepatic circulation prolongs the presence of the toxin in the serum, but rapid binding to protein causes the concentration of "free" amatoxins to decline rapidly after absorption. Amatoxins possess a high affinity to the surfaces of charcoal polymers in hemoperfusion cartridges.[14]

Clinical manifestations of *Amanita* poisoning can be separated into three clinical stages.[15,16] The initial stage of *Amanita* poisoning, beginning 6−24 hrs after mushroom ingestion, causes patients to experience nausea, vomiting, abdominal pain, cholera-like diarrhea, and hematuria. In the second stage, 12 to 48 hrs after ingestion, there is apparent clinical recovery, with the absence of symptoms. During the asymptomatic interval, subclinical hepatic and renal disturbances can be detected in the clinical laboratory by increases in the activity of aminotransferase, creatinine, and urea nitrogen in serum. Serum aminotransferase activity is the most sensitive, constant, and specific indicator of hepatocellular damage. During the third stage, 24 to 72 hours after ingestion, there is progressive and symptomatic hepatic and renal failure, coagulopathy, cardiomyopathy, encephalopathy, convulsions, coma, and death. Our three cases were consistent with these clinical courses. Case 2 patient eventually died even though her initial aminotransferase levels were less than 300 IU/L, but her PT was prolonged to 30 seconds. Case 1 and 3 patients survived, even though their initial aminotransferase levels were more than 4000 IU/L. Our cases showed that PT may be a better prognostic indicator than aminotransferase levels. Factor V also seemed to be a good prognostic marker, but not better than PT.

Amatoxins in fresh or dried mushrooms can be detected by a simple color reaction using hydrochloric acid,[17] but this test cannot be applied to aspirated gastric contents. Some chromatographic assays have been introduced.[18] However, identification of the mushroom, by examination of the implicated meal or gastric contents for typical morphology and spores, is most commonly used to help predict the clinical course and provide a guide for specific therapy.[3]

The major objectives of therapy are to lower the serum amatoxin concentrations as soon as possible.[3] Initial treatment, designed to eliminate ingested toxin, includes gastric lavage and the administration of emetics, activated charcoal, and cathartic. Hemoperfusion or hemodialysis removes limited amounts of toxin due to its rapid removal during the incubation period. Repetitive activated charcoal administration is recommended to block the enterohepatic circulation of toxin, even after the incubation period.[19] Preexisting renal insufficiency or renal hypoperfusion due to hypovolemia can delay renal excretion of toxin.[20,21] Urinary excretion should be maintained by vigorous hydration and/or diuretic therapies. Routine serum electrolyte disturbances due to diarrhea must be corrected. All three cases showed proteinuria from 1+ to 3+ on spot urinalysis at the time of presentation. Case 1 and 3 patients showed mixed, namely tubular (beta-2 microglobulin, lysozyme, and free light chain) and glomerular proteinuria, with high-resolution urine

SDS agarose gel electrophoresis (Fig. 1), which supported the tubular as well as glomerular damage by Amanita toxin. This damage seemed to be reversible, because the urinalysis of Case 1 and 3 patients became normalized 10 days and 5 days, respectively, after ingestion of the mushrooms, although we could not check the follow-up urinalysis. Identification of spot urine protein suggests early possible renal toxic insult, although not always accompanied by acute renal failure, and may be helpful not only for the differential diagnosis of this condition from simple acute gastroenteritis, but also for prompt management. Case 2 patient showed mild albuminuria and the lowest aminotransferase levels at the time of presentation, but she eventually died. So we cannot rule out *Amanita* poisoning in the case of no proteinuria at presentation as in the cases of Piering and Bratanow,[3] but close follow-up of urine protein level is essential. Whenever dipstick proteinuria is noted, its characterization by urine beta-2-microglobulin quantification or high-resolution urine SDS agarose gel electrophoresis[22] is recommended for the early identification of renal glomerular or tubular damage.

Penicillin, silymarin, and cimetidine are used in *Amanita* mushroom poisoning.[13,15] Cimetidine may prevent amanitin toxicity by competitively inhibiting cytochrome P450; as amanitins are believed to be converted to toxin metabolites by the hepatic cytochrome P450 system.[23] Thiocotic acid is controversial therapy.[15] Other proposed therapies include vitamin C, nifuroxazide, and dihydrostreptomycin.[3] Indications for hepatic transplantation include encephalopathy, uncorrectable severe coagulopathy, refractory hypoglycemia, and a serum total bilirubin level >25 mg/dL.[24-27]

Whenever mushroom poisoning is suspected, attempts should be made to identify the offending mushroom by sending some remains of the meals to an experienced mycologist to determine whether the ingested mushroom is toxic. Therapy should be started in any suspected cases as soon as possible, with close monitoring of blood volume, electrolytes, and liver and renal function tests to provide a guide for the necessary aggressive therapy.

ACKNOWLEDGEMENTS

We appreciate Mr. Seok-Cheon Hwang, M.P.H., Jinsung Meditech Co., for his kind demonstration of urine protein high-resolution SDS-agarose gel separation and the technical support of Mr. Kun Han Kim, M.T., Department of Clinical Pathology, Yongdong Severance Hospital.

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