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Coagulation disorders secondary to acute liver failure in Amanita phalloides poisoning: A case report

Amanita phalloides zehirlenmesinde akut karaciğer yetmezliğinden kaynaklanan koagülasyon bozuklukları: Olgu sunumu

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Amanita mushroom poisoning is a serious occurrence. Physicians need to recognize the syndrome promptly and institute effective treatment as soon as possible in order to avoid the often fatal complications. We report a case of a young man with mushroom poisoning of the genus Amanita with a clinical spectrum that ranged from hepatic failure and coagulation disorders to an outcome with a partial recovery. The aim of this report was to emphasize the clinical outcomes and treatment regimens in this type of mushroom poisoning seen with increasing frequency in our region.

Key words: Mushroom poisoning, hepatic failure, coagulopathy

Amanita türü mantar ile zehirlenme oldukça ciddi seyir gösterir. Ölümcül olabilen komplikasyonlarından korunmak için kısa sürede tanı koyulmalı ve tedavi başlanmalıdır. Olgumuz Amanita türü mantar ile zehirlenme sonucunda karaciğer yetmezliğine giren ve koagulasyon kaskadındaki bozulmadan kısmi iyilik haline uzanan bir klinik seyir gösteren genç bir erkekti. Amacımız bölgemizde gittikçe daha sık görülen bu tip mantar zehirlenmesinin kliniğini ve tedavi yöntemlerini vurgulamaktı.

Anahtar kelimeler: Mantar zehirlenmesi, karaciğer yetmezliği, koagulopati

INTRODUCTION

Mushroom poisoning is a medical emergency. Typically, wild mushroom poisoning is more frequent in Western Europe, with 50-100 fatal cases reported yearly. According to one report, <100 cases of fatal mushroom poisoning occurred in the United States between 1900 and 1994 (1). Cases of mushroom poisoning are quite frequent in the wooded areas of Central Tuscany, in Italy (2), and in Turkey (3, 4), including surroundings of İstanbul (5). The common culprit, member of the widespread and mostly edible genus Amanita, is Amanita phalloides, and most of the cases with Amanita poisoning are fatal (1-6).

The main characteristic of Amanita phalloides, a mushroom that grows in summer and autumn, is its high toxicity. Twenty to fifty grams of fresh mushroom can cause severe liver and kidney damage due to a series of low molecular weight polypeptides (amatoxins, phallotoxins, viroisin, viroidin), the most lethal of which are the amatoxins. The amatoxins, primarily the alpha and beta groups, are thermostabile and dialyzable octapeptides which bind to subunit of RNA-polymerase II or B and interfere with messenger RNA synthesis so that the protein content decreases and cell necrosis sets in. (2, 4, 6-8). This interaction inhibits the synthesis of messenger RNA in the hepatocytes, decreases the formation of coagulation factors and immunoglobulins and effects a vasoconstruction (6). Approximately 0.2 to 0.4 mg of the α-amanitin can be recovered from 1 g of fresh Amanita phalloides (8). Aside from the liver and kidney, other organs affected by α-amanitin include the pancreas, testis and blood (8). Viroisin, viroidin and the phallotoxins seem to be of minor toxicological importance; they consist of heptapeptides with rapid action but are generally regarded as inactive when taken orally (2).

Amanitin poisoning is characterized by four clinical stages: 1-incubation stage, 2- gastrointestinal

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stage, 3-cytotoxic stage and 4-comatose stage (1, 2, 4, 8).

Poisoning with the genus Amanita is common in Turkey because mushrooms are cooked before they are consumed and the other types of mushrooms, but not Amanita, lose their toxins if they are processed by heat (3).

We report a case of mushroom poisoning of the genus Amanita with a clinical spectrum that ranged from hepatic failure and coagulation disorders to an outcome with a partial recovery. The aim of this study was to emphasize the importance of this type of mushroom poisoning, seen with increasing frequency in our region, and its management.

CASE REPORT

A 36-year-old man from the countryside (Denizli, Güney County) presented with complaints of abdominal pain, nausea, vomiting, diarrhea, fever, weakness and ecchymoses on the extremities. He declared that 48 h prior to his admission to the hospital he had consumed approximately 50g of mushroom (three or four mushrooms) and 11-12 hours later he had developed severe abdominal pain, especially in the epigastric and right upper quadrant area, with nausea and vomiting.

On admission he was somnolent, with T: 38°C, RR: 32/minutes, PR: 110/minutes, regular, and BP: 70/40 mmHg. Except for sinus tachycardia, ECG was normal. Pupils were equal in size and reactive to light. Funduscopy was normal. Jugular venous pressure was normal. The skin was dry. Heart sounds and breathing sounds were normal, but he had tachypnea. His abdomen was soft with mild tenderness on the epigastric and right upper quadrant area. Bowel sounds were hyperactive. No organomegaly or ascites was found. There was no edema but large ecchymoses on the extremities were present. Cranial nerves and motor power were normal, and deep tendon reflexes were normoactive.

His initial blood chemistry values revealed severe electrolyte imbalance and worsening liver and renal function (potassium 5.6 mEq/L, phosphorus 5.8 mg/dl, calcium 5.9 mg/dl, sodium 128 mEq/L, chloride 93 mEq/L, AST 9960 U/L, ALT 4750 U/L, total bilirubin 4.06 mg/dl, direct bilirubin 1.52 mg/dl, serum albumin 3.63 mg/dl, alkaline phosphatase 135 U/L, LDH 22920 U/L, CK 4061 U/L, CK-MB 306 U/L, blood glucose 118 mg/dl, blood urea nitrogen 72 mg/dl, creatinine 2.89 mg/dl, uric acid 14.56 mg/dl and amylase 560 U/L). Urine sediment was normal. Serum hepatitis markers such as HBsAg, Anti-HBs, Anti-HCV and Anti-HIV were negative.

Hospital Course

His initial management included placement of a nasogastric tube for aspiration and administration of 60g charcoal every four hours. Simultaneously, fluid and electrolyte resuscitation to treat the copious diarrhea and emesis present in the course of intoxication, infusion of penicillin G in doses of 250 mg/kg/day, and hemoperfusion on activated charcoal for 3 h every day (CLARK: Biocompatible hemoperfusion cartridge; Sorbent: heparinized polymer over activated carbon, 250 ml) were started (1, 4, 6, 8, 9).

On the second day of his admission his temperature rose to 39°C. The hemostatic parameters were: PT 25.5 seconds, INR 2.26, aPTT 28.4 seconds, serum fibrinogen 210 mg/dl, D–dimer 1355 ng/ml (N <500 ng/ml) and platelets 72000/mm^3. Transfusion of fresh frozen plasma from 15 ml/kg was started to correct the coagulopathy. On the third day of his admission methicillin-resistant Staphylococcus aureus was established in the hemoculture. White blood cell count was 22000/mm^3 in the hemocount, with 75% segmented neutrophils and 10% bands. His arterial blood gas values revealed a metabolic acidosis with a pH of 7.25 and bicarbonate concentration of 11 mmol/L. The condition was related with the systemic infection, and vancomycin (2 x 1 g daily) was started under strict control of creatinine clearance, which was 75 ml per minute at the time. We stopped antibiotic treatment by day 12 after the control hemocultures were negative. Abdominal sonography showed a hyperechogenic liver with a coarse parenchyma, suggestive of acute parenchymal damage. The renal parenchyma were normal. No ascites was found.

In spite of all supportive measures his condition deteriorated. His prothrombin time prolonged to 30 seconds, INR was 3.1, aPTT 36 seconds, D–dimer over 1500 ng/ml, functional antithrombin III (ATIII) 13.8% (70–150), immunologic AT III 17.6 mg/dl (24.9-33.1), protein C 40.92% (70– 30), protein S 61.4% (70–130), factor V 72% (70-120) and Factor VIII 60% (50-170). Peripheral cyanosis especially around the digit tips of the lower extremities was evident.

By day 4, there were visual disturbances. Pupils were reactive to light. Visual acuity of the left eye

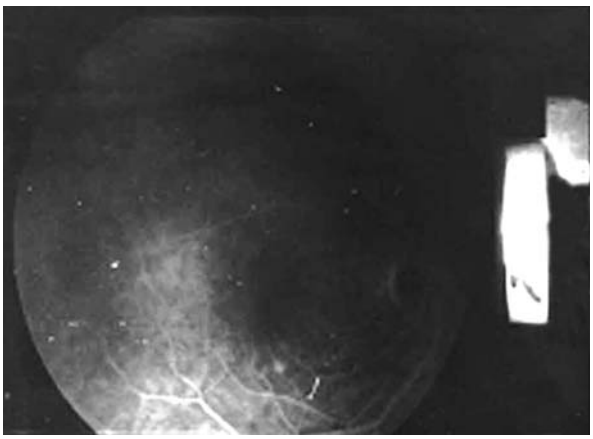

Figure 1. Fundus fluorescein angiography (FFA) showed an early delayed arterial phase and an ischemic retina in the late phase of angiography

decreased to only light sensation and the right eye to hand motion in a few meters. Fundus fluorescein angiography (FFA) showed an early delayed arterial phase and an ischemic retina in the late phase of angiography (Figure 1). The fundus was pale on funduscopy, and hemorrhagic fields were seen in the retina (Figure 2).

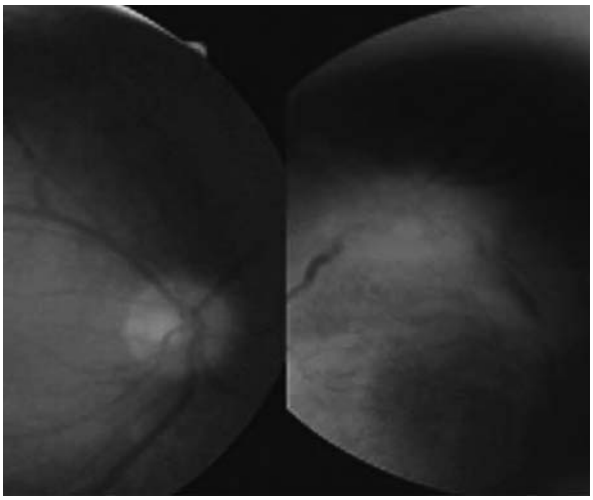

Figure 2. Right: Normal fundus. Left: Ischemic fundus of the patient

By day 7, neurologic deficits such as hemiplegia and positive Babinski sign of the right side were discovered. The cranium MR showed an early phase infarction at the left median artery area with edema and compression of the lateral ventricle

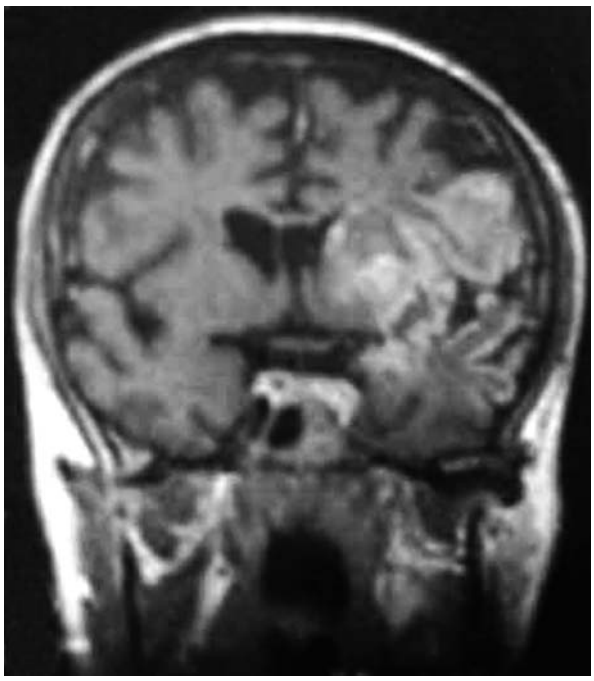

Figure 3. Cranium MR showed an early phase infarction at the left median artery area with edema and compression of the lateral ventricle

(Figure 3). At this time necrotizing lesions over the digit tips of the lower extremities became apparent (Figure 4), and arteria dorsalis pedis and arteria tibialis posterior of both lower extremities were inadequately pulsatile by Doppler ultrasound.

The patient was treated vigorously with vitamin K (10 mg/day), lactulose, branched chain amino acid solution (hepatamine) and 10% dextrose

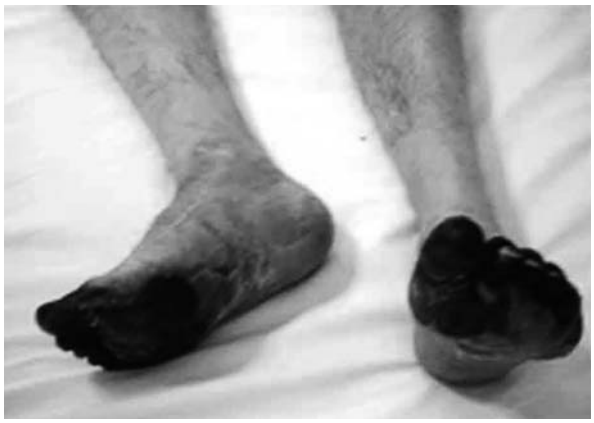

Figure 4. Necrotizing lesions over the digit tips of the lower extremities due to coagulopathy

intravenously for acute liver failure, and with fresh frozen plasma (15 ml/kg/day) to correct the coagulopathy. Rheomacrodex infusion 500 cl daily for 5 days and salicylate 100 mg daily were started for distal arterial thromboembolic lesions. The administration of crystalloid was kept to a minimum during this stage of liver failure so as not to be more catastrophic on the encephalopathy (cerebral edema). Activated charcoal via nasogastric tube continued for five days and charcoal hemoperfusion continued for 10 days, penicillin G infusion continued for two weeks, and intravenous hydration continued until he was discharged. His liver function tests improved substantially. The neurologic status improved with decreasing lethargy but hemiplegia and visual disturbances were left as sequelae. By day 25, after his hemostatic parameters and renal and liver function tests normalized, he was amputated from the ankle of his right leg and last three digits of the left leg. He was discharged home by day 36.

DISCUSSION

Cases of mushroom poisoning are quite frequent in Turkey. Poisoning by cytotoxic mushrooms (Amanita phalloides and related species) is associated with severe morbidity and high mortality rate (lethality >20% in adults and >50% in children) (6, 10). Once a diagnosis of acute Amanita phalloides poisoning has been established, the patient's care is mainly supportive, as no specific antidote exists for its toxins (1, 2, 6, 8-10). Because of the latency period in the development of symptoms, treatment should begin on the first suspicion that an intoxication is present. The best therapeutic results can be expected when the detoxification techniques are applied in combination with conservative therapies within the first 36-48 h. Using this approach, mortality rates in some recent studies have been below 10% (10). Our patient had the physical and laboratory signs of the gastrointestinal stage of Amanita poisoning characterized by abdominal pain, diarrhea and vomiting on admission, two days after his consumption of mushrooms. His low blood pressure, tachycardia, fever and deteriorated biochemical values reflected dehydration and electrolyte loss secondary to emesis and diarrhea, worsening of liver and renal functions and bacteriemia. We could not find any origin for the bacteriemia of methicillin-resistant Staphylococcus aureus; it might have been related to the intravenous catheter used for fluid replacement before admission to our hospital. The origin of methicillin-resistant Staphylococcus aureus bacteriemia cannot be found in one-third of the cases or it may depend on extravascular or intravascular foci, such as IV catheters (11). The cholera-type diarrhea seen most commonly as an effect of phalloidin during the first 24 hours of illness can produce a profound metabolic alkalosis requiring vigorous fluid resuscitation and electrolyte replacement (8). However, the metabolic acidosis together with low platelets and increasing D-dimer in this case were related to the bacteriemia followed by disseminated intravascular coagulation (DIC), as is emphasized (11). Tissue factor exposure to blood is the most common trigger of DIC. This can occur during Gram-positive infections like in our case. Several underlying disorders (e.g. liver disease-related coagulation abnormalities) can affect the hemostatic parameters and can lead to a false-positive diagnosis of DIC (12).

During the third, or cytotoxic stage, clinical and biochemical evidence of liver damage became evident. Liver function tests and coagulation studies rapidly became abnormal. This stage occurred approximately 48 hours after the patient ingested the mushroom. The hepatic necrosis became manifest by rapidly advancing encephalopathy and a profound coagulopathy. The decrease in the activity of AT III, protein C, protein S, factor V, factor VIII and serum fibrinogen levels resulted in prolonged prothrombin time and activated partial thromboplastin time. It was noted that the most reliable indicator as to the severity of Amanita poisoning is the prothrombin time (8, 13), and factor V is a better indicator of the recovery of liver synthesis function than other factors (13). Renal failure is caused by hepatorenal syndrome and/or by the direct nephrotoxicity of α–amanitin (1, 8) resulting in oliguria. Neurologic disorders are attributed to the direct neurotoxic effect of α–amanitin and the brain edema of acute liver failure (1, 8).

The renal function of the patient improved by day 5, but hepatic, neurologic and visual functions deteriorated with signs and symptoms of coagulopathy. FFA and cranium MR supported emboli that were related to coagulopathy in the etiology of the visual and part of the neurologic disturbances. The clinical manifestations were not explained by the decrease in half-lives of coagulation factors and inhibitors alone, but also by DIC with

multiorgan dysfunction caused by microthrombi and bleeding due to consumption of platelets, fibrinogen, factor V and factor VIII (12).

The patient had a slow resolution as a result of treatment with charcoal hemoperfusion and other supportive measures to prevent the absorption of amanitin toxins into blood. His initial therapy consisted of gastric lavage (regardless of the time of presentation), intensive intravenous fluid resuscitation, and activated charcoal via nasogastric tube to remove all remaining stomach contents and to draw the toxin from the enterohepatic circulation. The use of multiple doses of charcoal has theoretical value in this regard, although there are no definitive studies of its usefulness (1, 4, 6, 8, 10). A number of drugs have been tried with varying success in Amanita mushroom intoxication. Penicillin G in doses of 250,000 to 1,000,000 U/kg/day has been recommended, (1, 4, 8, 9) for its ability to displace amanitin from plasma protein binding sites and thus allow for increased renal excretion, to prevent the hepatic uptake of the amatoxin and to kill certain enteric bacteria that produce gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter metabolized in liver failure and implicated in hepatic encephalopathy (1, 8, 9). Silibinin, another drug that has cytoprotective abilities against amatoxin (1, 8), could not be used in this case due to its non-availability in Turkey. Vitamin K and FFP are often given to supplement clotting factors in severe coagulopathy (8, 12), and both were applied in this case.

Several studies have suggested that early hemoperfusion (<24 hours after exposure) over a charcoal filter should be considered if patients fulfill the criteria of time from ingestion, biochemical evidence of toxicity, ingestion of a potentially lethal dose (>50 g of Amanita mushroom in an adult), and an elevation in serum enzymes (14). Hemodialysis may also be used, but may be less effective (6). Recently, a new detoxication method referred to as MARS was introduced for protein–bound substances in patients with liver failure and grade II and IV hepatic encephalopathy. The method depends on an albumin-containing dialysate which is recycled in a closed loop that contains a charcoal cartridge, an anion exchanger resin adsorber and a conventional hemodialyzer (6). With dialysis using an albumin-containing dialysate, protein-bound substances, which are usually not sufficiently dialyzable, can be eliminated, even as late as up to a week after mushroom ingestion.

We report a case of Amanita phalloides ingestion presenting with a spectrum of clinical manifestations that ranged from acute liver failure to severe coagulation disorders. We believe that the best therapeutic results can be expected when detoxification techniques are applied in combination with conservative therapies within the first hours; orthotopic liver transplantation should be considered in patients who progress to hepatic encephalopathy with significant and worsening derangement of both clotting factors and elevation in the liver enzymes.

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