ABSTRACT
The clinical picture secondary to amanita phalloides, which began with gastrointestinal complaints, advanced to fulminant hepatic failure in two days. Emergency liver transplantation was decided for the case of a 48-year-old male patient, who at the same time had renal failure and acute pancreatitis. Bridge treatment with plasma diafiltration was applied until the liver transplantation, which was successfully performed on the fifth day of admission to the hospital. Acute pancreatitis and renal failure also resolved and the patient was discharged in a healthy condition on the 30th day of admission. The timing of the transplant in fulminant liver failure and criteria used to select the timing are particularly important. Transplantation should be performed not too early, nor too late. In addition, the development of multiple organ failure during the period until transplantation may result in the death of the patient. Therefore, extra corporeal liver support systems are suggested as an important treatment tool at this stage.

Key words: Amanita phalloides, Fulminant liver failure, plasmapheresis, transplantation

INTRODUCTION
Amanita phalloides (AP) poisoning might result in mild gastrointestinal complaints, such as nausea, vomiting, abdominal pain, and diarrhea; however, severe poisoning can occur with only one mushroom intake and may result in acute liver failure (ALF) in some cases, necessitating liver transplantation (1,2). The mortality rate has been reported to be 2-22% in the literature (3,4). On the other hand, early transplantation carries its own risks.

The aim of this study is to discuss the criteria for the decision of transplantation and bridge treatment applied in the period until transplantation in a case of ALF.

CASE
A 48-year-old male patient presented to the hospital with complaints of vomiting and diarrhea eight hours after the ingestion of wild mushrooms that he had col-
Fulminant liver failure due to amanita phalloides

The case is summarized below.

During his stay in the ICU, the patient received 18 units of fresh frozen plasma (FFP) through transfusion, three units of platelet suspension, and three units of erythrocyte suspension during his stay in the ICU. The clinical progress of the case is summarized below.

**Day 3:** FFP in a dose of 15 mL kg-1 and vitamin K (20 mg menadione, intravenously) were administered. The plasma ammonia level was very high (736 µ dL-1) and the patient was given ornithine-aspartate (20 g day-1) and lactulose (45 g day-1), which continued for two days. PDF (Evacio EC-2C®) was applied for 6 hours with a blood flow rate of 200 mL min-1 and a plasma exchange rate of 2.5 L h⁻¹. Laboratory test results of the patient after the first session of PDF is shown in Table 1 (60th hour).

Continuous renal replacement therapy (CRRT) was started following the first session of PDF since the patient had anuria for approximately 12 hours (AKIN-classification of acute kidney injury-Stage III). Continuous venovenous hemodiafiltration (CVVHDF) was performed as a CRRT modality. CVVHDF was regulated as such so that the blood flow rate, dialysate flow rate, and replacement flow rate were 140 mL min⁻¹, 1000 mL h⁻¹, and 1000 mL h⁻¹, respectively; and ultrafiltration, although variable, was regulated to a rate of approximately 200 mL h⁻¹. Anticoagulation agents were not administered.

**Day 4:** The second session of PDF was performed. Laboratory test results of the patient prior to the second session of the PDF (at the 73rd hour) and after treatment (84th hour) are shown in Table 1. CRRT treatment was continued following PDF (Table 1). An imaging compatible with pancreatitis was obtained by abdominal tomography, which was performed due to an elevation of amylase (1648 U L⁻¹) and lipase (1524 U L⁻¹) values. His oral feeding was stopped and enzymes were followed-up.

**Day 5 after AP intake:** Bilirubin values of the patient were elevated to quite high levels (Table 1). A donor with a suitable match emerged and the patient underwent a cadaveric liver transplantation with an hepatic phase of 35 minutes at the end of day 5 after AP intake. The patient was extubated at the end of the operation. Postoperative Period: Non-invasive mechanic ventilation and CRRT were continued during the postoperative period. INR, AST, ALT, LDH, bilirubin, ammonia, amylase, and lipase levels resolved to normal values on the postoperative period (Table 1). CRRT continued until postoperative day 8. The patient was transferred to the ward from the ICU and was taken to the conventional hemodialysis program. Acute renal failure also resolved and the patient was clinically well at the time of discharge.
DISCUSSION

The clinical picture of gastroenteritis that developed after AP mushroom intake rapidly progressed to ARF and multiple organ failure. Emergent liver transplantation was planned based on the score of the patient according to King’s criteria. Bridge treatment with PDF was applied until a suitable donor was found for transplantation. A successful liver transplantation with a cadaveric liver was performed on day 5 of the AP intoxication. The patient was clinically well and discharged on day 30 of his admission to the hospital following the resolution of his renal failure, which lasted for some time. Phallotoxin, one of the toxins in the AP mushroom, changes the cell membrane of the enterocytes and results in clinical findings such as diarrhea, colicky abdominal pain, and vomiting 8-12 hours after ingestion of the mushroom. Amanitin, on the other hand, which mainly results in toxicity, inhibits protein synthesis. It rapidly degrades the gastrointestinal system cells, mainly the liver cells in which the rate of protein synthesis is high, primarily by enterohepatic circulation and proximal tubular cells of the kidneys (9). This explains the cause of the renal failure and pancreatitis that developed in addition to the fulminant hepatitis in this case. The number of cases reported with acute pancreatitis after AP intake is quite limited, although fulminant hepatitis and renal failure are frequently reported (2,10). Renal failure is associated with the direct toxic effect of alpha amanitin or with hepatorenal syndrome. The development of acute pancreatitis after AP intake has been reported to occur much earlier after the ingestion of the toxin (10).

In the current case, the clinical picture of acute pancreatitis developed four days after AP intake; enzyme elevation lasted for some time and then it returned to normal levels.

The toxin in AP intoxication can be detected by the radioimmunoassay method in blood, urine, and gastric fluid. The level of the toxin decreases to an amount that can no longer be detected in plasma 36-48 hours after ingestion of the toxin; however, it can be detected in the urine for 96 hours (11). Toxin levels were not measured in this case; the diagnosis was made on the basis of anamnesis and clinical findings of the patient.

One of the primary aims of the treatment is to decrease hepatic damage by preventing the uptake of the toxin in the cells. Some of the initial effective methods in the treatment are gastric lavage, oral administration of activated coal, cholestyramine, and Ipecac syrup administered 30 minutes after ingestion (12). These treatment modalities were not applied since the patient was admitted to our clinic 48 hours after AP ingestion. N-acetylcysteine, high dose crystallized penicillin, and silibinin administration in the early period after the toxin ingestion have been recommended. Although there are no differences in the rate of transplantation and mortality between silibinin and combined silibinin and penicillin treatment, the combined treatment has been generally used in clinical practice (13). The researchers of the current study also used the same treatment. Fluid resuscitation and providing a urine output of 100-200 mL h⁻¹, especially for the first 4-5 day, increased the renal elimination of the toxin (14). CRRT was performed and continues in the postoperative period in this case, since no urine output was present starting from the first hours after admission.

One of the controversial issues in the case of AP toxicity is the timing of transplantation if an acute liver failure develops. If it is performed too early, questions may arise among the medical staff such as, “Did we do it too soon?"
early, could we have waited a little longer?" A decision to transplant that yields poor results elicits some issues such as the side effects of immunosuppression, the mortality of surgery, loss of a graft that could be used for an elective transplantation, and unnecessary costs. On the other hand, the issues that might be encountered when the timing of transplantation is delayed are a donor that is no longer available, the development of contraindications for transplantation, and loss of the patient (15,16). The validity and feasibility of many criteria for the current use of the selection of the treatment modalities are debatable (17,18). The most commonly used criteria among those are the King’s College criteria. The decision for transplantation was made based on the King’s College transplantation criteria in this case (INR value greater than 6.5 at the time of admission).

Another classification system for transplantation indication is the Clichy criteria (19,20). This classification is based on the age and the plasma factor 5 level. The inapplicability of plasma factor 5 detection in some centers limits the use of Clichy criteria (19,20). The King’s College criteria have been found to be superior to Clichy and Ganzert criteria in the detection of fatal progress due to A. Phalloides ingestion in many studies (14,16). Non-paracetamol ingestion among the King’s College criteria were reported to detect the fatal progress earlier (16). In addition, independent of all other variables, urgent transplantation should be considered in cases with a prothrombin index of less than 10% of normal (INR greater than 6) four days or more after the ingestion of the mushroom (16). These specific criteria were determined by Ferraira et al. as the most accurate (100%) criteria for urgent liver transplantation in ALF induced by AP. An INR value of 7.2 at the 48th hour in the present case required urgent transplantation according to these criteria.

Among the fatal risk factors for intoxication are eight hours or a shorter period from mushroom ingestion to start of the diarrhea, elevation of lactate at admission, biphasic elevation pattern of transaminases, prothrombin index, and even the lowest INR value higher than normal (6,16). The lag period from mushroom ingestion to start of the diarrhea was approximately eight hours, lactate was elevated at admission, and transaminases were elevated and INR was high in spite of FFP transfusion in the case presented herein. All of the above facts can be accepted as signs of poor prognosis (Table 1).

Recently, the use of support systems applied with the aim of increasing survival without transplantation or providing a bridge function until transplantation have generally been reported in cases of acute liver failure (7). PDF has also been used for this purpose, although Molecular Adsorption Recirculation System (MARS) and Fractionated Plasma Separation and Adsorption (FPSA-Prometheus®) systems have been the most frequently selected treatment modalities for bridge treatment (21,22). In spite of only two sessions of the application of PDF in this case, its benefits are more prominent in repeated applications. It was used successfully to support the deteriorating liver functions and treat itching until retransplantation in a patient with prior orthotrophic liver transplant, who presented with complaints of jaundice, itching, and renal failure due to rejection (23). This system provides an option to clear the albumin-bound and water soluble toxins. It clears the plasma components with the help of a filter depending on the dimensions of the components. A selective membrane separator is used with a 100 kDa cut-off (Evaclio EC-2C) value. Dialysis is also performed in addition to selective plasma type in PDF. PDF has a greater capacity of excretion of toxic solutes compared with simple selective plasma filtration. Furthermore, its total costs and training requirements are less compared to MARS and Prometheus (21,23).

In conclusion, ALF, renal failure, and acute pancreatitis may develop due to the ingestion of A. Phalloides. Therefore, such a patient should be closely monitored, starting from the first hours after ingestion of the mushroom and should be transferred to a transplant center in the case of poor clinical progress. Poor prognostic factors should be taken into consideration in addition to specific criteria used to decide to transplant the case, although it is not an easy decision to make. Plasma dialfiltration can be used as an option for bridge treatment to gain time and to prevent mortality. However, further studies are required on this issue.

REFERENCES
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