Renal Replacement Therapy

CASE REPORT

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Three cases of mushroom poisoning with an unexpected initial presentation: acute kidney injury with *Amanita proxima* poisoning

Mehmet Fethullah Aydın[1*], Mehmet Sezen[1], Aysegül Oruç[1], Abdülmecit Yıldız[1], Kübra Özerik[2], Hatice Aslan[2], Can Özgü[2], Elif Özge Kuş[2], Ferda Kahveci[3] and Alparslan Ersoy[1]

Abstract

Background Mushroom poisoning causes common gastrointestinal symptoms such as nausea and vomiting and is a well-known reason for acute hepatic failure. Acute kidney injury is a less common clinical presentation in mushroom poisoning. Recently, nephrotoxicity called Amanita nephrotoxic syndrome has been defined, caused by several *Amanita* mushrooms. It is characterized by moderate hepatotoxicity and oligoanuric acute kidney injury, which may require hemodialysis.

Case presentation Case 1 was a 51-year-old female patient who was hospitalized with oliguria, nausea, and vomiting after eating mushrooms, required hemodialysis due to acute kidney injury, and developed pulmonary hemorrhage during her follow-up. Case 2 was a 55-year-old male patient who was hospitalized with anuria, nausea, and vomiting after eating mushrooms, required hemodialysis due to acute kidney injury, and developed acute coronary syndrome during his follow-up. Case 3 was a 59-year-old male patient who was hospitalized with oliguria, nausea, and vomiting after eating mushrooms, required hemodialysis due to acute kidney injury, and developed moderate hepatotoxicity during his follow-up. All cases were hospitalized at the same time interval with similar clinical features. Acute kidney injury was the initial presentation of all the cases, and they had only mild transaminase elevation with normal INR levels. They all required hemodialysis, and kidney injury was fully recovered.

Conclusions Mushroom consumption must be questioned in acute kidney injury patients of unknown etiology where mushrooms are habitual despite deleterious consequences.

Keywords Acute kidney injury, *Amanita proxima*, Amanita nephrotoxic syndrome, Mushroom poisoning, Nephrotoxicity

Background

Mushroom poisoning can lead to several organ failures and may cause death. *Amanita* mushrooms, which contain amatoxin, are responsible for more than 90% of deaths caused by mushroom poisoning [1, 2]. The initial symptoms of mushroom poisoning are usually nausea and vomiting within 6 h after consumption. Subsequently, hepatic failure and occasionally kidney injury accompanies. Hepatic failure is the leading initial presentation of mushroom poisoning usually caused by *Amanita* mushrooms. Classically kidney injury is due

*Correspondence:
Mehmet Fethullah Aydın
mfaydin@uludag.edu.tr; mfaydin@gmail.com
[1] Division of Nephrology, Faculty of Medicine, Bursa Uludağ University, Nilüfer, Bursa, Turkey
[2] Department of Internal Medicine, Faculty of Medicine, Bursa Uludağ University, Bursa, Turkey
[3] Department of Anesthesiology and Reanimation, Faculty of Medicine, Bursa Uludağ University, Bursa, Turkey

to dehydration and direct nephrotoxicity [3]. However, acute kidney injury is an infrequent initial presentation of mushroom poisoning. In the early 1990s, a novel mushroom poisoning with the prominence of acute kidney injury called *Amanita* nephrotoxic syndrome was defined, which was caused by other *Amanita* mushrooms like *Amanita smithiana* and *proxima* [3–11]. *Amanita* nephrotoxic syndrome is characterized by gastrointestinal symptoms of abdominal pain, diarrhea, nausea, and vomiting within 6–24 h after consuming mushrooms, moderate hepatotoxicity, and oligoanuric tubulointerstitial nephritis [5]. Treatment strategies consist of supportive treatment and dialysis if required. Although there is no evidence of the efficacy of detoxifying procedures like beta-lactam antibiotics, silymarin, N-acetylcysteine, they could be used.

Herein, we presented a case series of three patients diagnosed with *Amanita* nephrotoxic syndrome in the same period who bought mushrooms from the same street market.

Cases

Case 1

A 51-year-old female with no systemic disease was admitted to the emergency department with oliguria, nausea, and vomiting. She had no history of using herbal medicine or other nephrotoxic agents. Three weeks ago, she used favipiravir for ten days because of coronavirus disease 2019 (COVID-19) infection, and she recovered with no history of pneumonia. Her blood pressure was 125/75 mmHg, and there were no positive findings on his physical examination. Laboratory findings revealed serum urea 86 mg/dL, creatinine 7.5 mg/dL, glucose 96 mg/dL, AST 79 U/L, ALT 285 U/L, LDH 1318 U/L, normal INR, and moderate acidosis with a venous pH 7.29, HCO_3 17.3 mmol/L. In the urinary analysis, protein was negative, glucose was 2+ with a density of 1005, and 5/HPF erythrocytes, 25/HPF leukocytes. The renal ultrasound was normal. She was hospitalized with the diagnosis of prerenal acute kidney injury and urinary tract infection, and empirically ceftriaxone was started. She stated mushroom consumption five days ago, which she bought from the street market, and severe nausea and vomiting after five hours of mushroom consumption. There were no similar features among other family members. Differently from family members, the patient ate leftover mushrooms the next day. With the diagnosis of mushroom poisoning, charcoal hemoperfusion was performed, 20 mg/kg/day silymarin infusion and 1800 mg/day N-acetylcysteine were started. On the third day, she was electively intubated because of respiratory failure with acidosis, hypoxemia, and hypercapnia (pH: 6.94, pCO_2: 65.4 mmHg, pO_2: 68.6 mmHg, HCO_3: 10.4 mmol/L, lactate: 55 mg/dL). She had a hemorrhagic tracheal aspirate. Pulmonary edema and/or alveolar hemorrhage was detected in thoracic computed tomography. COVID-19 PCR was negative. A 1000 mg methylprednisolone was administered. Meropenem and linezolid were started, and continuous venovenous hemodiafiltration (CVVHDF) was performed at the intensive care unit. After a total of three days of CVVHDF, her diuresis gradually increased, and she did not need dialysis during follow-up. Pulmonary renal syndromes were excluded with negative ANA, ANCA, and anti-GBM results. On the 21st day of hospitalization, she was discharged with a serum creatinine of 1.17 mg/dL and normal transaminase levels. After three weeks and five months, her laboratory findings were all normal on the outpatient clinic visit.

Case 2

A 55-year-old male was admitted to the emergency department with anuria, hiccups, nausea, and vomiting. His blood pressure was 120/70 mmHg, and there were no positive findings on his physical examination. Laboratory findings revealed serum urea 237 mg/dL, creatinine 17.08 mg/dL, glucose 93 mg/dL, AST 23 U/L, ALT 142 U/L, LDH 617 U/L, normal INR, and moderate acidosis with a venous pH 7.2, HCO_3 9.9 mmol/L. In the urinary analysis, protein was negative, and glucose was 3+ with a density of 1010. Renal ultrasound was normal, and his past medical history was negative. He had no history of using herbal medicine or other nephrotoxic agents. Hemodialysis was performed because of anuria, acidosis, nausea, and vomiting. On the second day, he complained of angina, and negative T waves were seen on V1 to V6, D1, and aVL derivations. Acute coronary syndrome was diagnosed with elevated Troponin-I levels. Metoprolol, atorvastatin, antiaggregant treatment with acetylsalicylic acid and clopidogrel were started. The ejection fraction was %55, the inferior wall was hypokinetic, and there was mild mitral and tricuspid regurgitation at his echocardiography. Coronary angiography was planned after amelioration of the acute kidney injury. After three hemodialysis sessions, urinary output increased gradually. He was hospitalized before the first case. Since mushroom poisoning was diagnosed in the first case, we questioned our patient, who had the same findings in terms of mushroom consumption. He declared mushroom consumption five days ago and severe nausea and vomiting after 8 h of mushroom consumption. There were no similar features among other family members. Similar to the first case, he ate leftover mushrooms the next day, unlike his family members. He was discharged on the 17th day with serum urea of 56 mg/dL, creatinine of 1.86 mg/dL, and normal transaminase levels with supportive treatment. After two and nine months,

his laboratory findings were all normal on the outpatient clinic visit.

Case 3

A 59-year-old male was admitted to the emergency department with oliguria, hiccups, nausea, and vomiting. He had diabetes mellitus for 13 years, hypertension for five years, and ischemic heart disease. His blood pressure was 140/65 mmHg. He consumed mushrooms from the street market three days ago and had severe nausea and vomiting after 6 h of mushroom consumption. There were no similar symptoms among other family members. Like the two patients mentioned above, he ate leftover mushrooms the next day. Laboratory findings revealed serum urea 134 mg/dL, creatinine 8.45 mg/dL, glucose 146 mg/dL, AST 40 U/L, ALT 139 U/L, LDH 1292 U/L, normal INR, and moderate acidosis with a venous pH 7.2, HCO_3 14.6 mmol/L. Urine analysis showed 60 leukocytes and 900 erythrocytes per HPF. Glucose was 4+in the urine analysis, whereas serum glucose was 110 mg/dL. The renal ultrasound revealed normal findings. He required hemodialysis because of acidosis (pH: 7.08) and hyperkalemia (K: 7.3 mmol/L). Mushroom poisoning was diagnosed. Afterward, transaminase and INR levels increased (AST: 334 U/L, ALT: 608 U/L, INR: 1.8). Hemoperfusion was performed, and 20 mg/kg/day Silymarin infusion, 150,000 IU/kg penicillin-G infusion, and 1800 mg/day N-acetylcysteine were started. After four sessions of hemodialysis and two sessions of plasma exchanges, the laboratory findings were ameliorated, and diuresis increased. He was discharged on the 19th day with a serum creatinine of 2.16 mg/dL and normal transaminase levels. After ten days and three months, on the outpatient clinic visit, his serum creatinine was 1.59 mg/dL and 1.15 mg/dL, respectively, and other laboratory findings were all normal.

Summaries of the clinical and laboratory findings of the patients are given in Tables 1 and 2.

Discussion and conclusions

Classically, mushroom poisoning with amatoxin is usually accompanied by acute liver failure and mild renal damage, which is considered to be a consequence of prerenal factors. Lately, there have been several reports of nephrotoxic *Amanita* species characterized by mild hepatotoxicity and severe acute kidney injury. We reported 3 cases of *Amanita* nephrotoxic syndrome admitted at the same time interval with similar clinical features. Acute kidney injury was the initial presentation of all the cases, and they had only mild transaminase elevation with normal INR levels. They all required hemodialysis, and kidney injury was fully recovered.

Renal damage is a component of mushroom poisoning. Besides *Amanita* nephrotoxic syndrome, usual mushroom poisoning with *A. phalloides* renal damage is mild to moderate due to prerenal factors, tubular

Table 1 Symptoms and onset times of the cases, HD requirements, and other pathologies developed during follow-up

	Age, sex	Symptom onset (h)	Initial symptoms	Admission time (d)	HD requirement	Other pathologies developed during follow-up
Case 1	51, F	5	Nausea, vomiting, oliguria	6	CVVHDF (3 days)	Moderate hepatotoxicity, alveolar hemorrhage, cardiac arrest
Case 2	55, M	8	Nausea, vomiting, hiccups, anuria	6	3 sessions	Moderate hepatotoxicity, acute coronary syndrome
Case 3	59, M	6	Nausea, vomiting, hiccups, oliguria	2	4 sessions	Moderate hepatotoxicity

M, male; F, female; HD, hemodialysis; and CVVHDF, continuous venovenous hemodiafiltration

Table 2 Laboratory findings of the cases on admission and discharge

	Laboratory findings on admission					Laboratory findings on discharge			
	Urea/Cr (mg/dL)/(mg/dL)	AST/ALT (U/L)	LDH (U/L)	INR	Urine analysis	Urea/Cr (mg/dL)/(mg/dL)	AST/ALT (U/L)	LDH (U/L)	INR
Case 1	86/7.5	79/285	1318	0.9	SG:1005, 2+ glucose, RBC:5/HPF, WBC:25/HPF	44/1.17	15/19	298	1.07
Case 2	237/17.08	23/142	617	1.11	SG:1010, 3+ glucose, RBC:0/HPF, WBC:8/HPF	56/1.86	17/30	126	0.9
Case 3	134/8.45	40/139	1292	1	SG:1019, 4+ glucose, RBC:900/HPF, WBC:60/HPF	64/2.16	24/47	273	1.27

Cr, creatinine; SG, specific gravity; RBC, erythrocyte; WBC, leukocyte, HPF, high-power field

Table 3 *A. proxima* literature review: Presentation, laboratory findings, hemodialysis requirement, and renal outcome

	Age, sex	Symptom onset (h)	Initial symptoms	Admission time (h)	Laboratory findings on admission		Laboratory findings on discharge		HD requirement	Renal outcome
					Urea/Cr (mg/dL)/(mg/dL)	AST/ALT (U/L)	Urea/Cr (mg/dL)/(mg/dL)	AST/ALT (U/L)		
#1 [6]	34, F	18	Nausea, vomiting, oliguria	48	NA/7.8	120/300	NA/1	18/12	10 days	Recovered
#2 [13]	45, F	8	Nausea, vomiting, heartburn	12	240/13	240/350	73/2.2	35/37	5 days	Recovered
#3 [14]	67, M	10	Nausea, vomiting, diarrhea, anuria	48	154/8.7	Mild elevated	Recovered	NA	9 sessions	Recovered

F, female; M, male; Cr, creatinine; NA, not available, AST, aspartate aminotransferase, ALT, alanin aminotransferase, HD, hemodialysis

damage of amatoxin, and fulminant hepatic failure [12]. Additionally, *Cortinarius* species may induce severe acute kidney injury causing patients to be dialysis-dependent. *Amanita* nephrotoxic syndrome was recently defined. It is characterized by nausea and vomiting 2–12 h and kidney injury 2–6 days after the mushroom consumption [11]. There are few reported cases of *A. proxima* [6, 13–15]. Reported cases of A. proxima are summarized in Table 3. In *Amanita* nephrotoxic syndrome, kidney injury is typically reversible, and approximately in 3 weeks, renal dysfunction is entirely resolved. That is why a renal biopsy is rarely performed. Kirchmair et al. reported 3 cases of *Amanita* nephrotoxic syndrome with *Amanita* mushrooms in whom renal biopsies showed acute interstitial nephritis and tubular necrosis [11]. In line with the literature, our cases were admitted to the hospital because of oligoanuric acute kidney injury after 2 to 6 days of consumption. In our cases, gastrointestinal symptoms began within 5–8 h. We diagnosed mushroom poisoning of *Amanita* species with the presentation of mild hepatotoxicity and severe reversible acute kidney injury. We considered that acute kidney injury resulted from tubulointerstitial damage accompanied by glycosuria, sterile pyuria, and microscopic hematuria. Renal biopsy was not performed because kidney injury was fully recovered in all cases. The striking feature of our patients was consuming the leftover mushroom the day after, which was also previously reported in a case of *A. proxima* poisoning [6]. It is speculated that the severity of symptoms is associated with the quantity of consumption [16].

The *A. smithiana* is a well-known nephrotoxic mushroom that leads to *Amanita* nephrotoxic syndrome. Furthermore, several *Amanita* species are causing *Amanita* nephrotoxic syndrome, regardless of having *A. smithiana* toxin [11]. *A. Proxima* is one of the mushrooms which of consumption manifests as *Amanita* nephrotoxic syndrome [6–8]. However, *A. proxima* does not consist *A. smithiana* toxin [11]. *A. smithiana, A. proxima, A. pseudoporphyria, A. abrupta, A. gracilior, A. echinocephala* with allenic norleucine (2-amino-4,5-hexadienoic acid) mycotoxin causes *Amanita* nephrotoxic syndrome with an unknown mechanism of renal toxicity [9]. Defining the causative mushroom cannot be possible every time. At the time of diagnosis of mushroom poisoning, we asked for leftover mushrooms to all our patients if available, but none of them could provide a sample. Furthermore, we looked for the supplier at the same street market. Although we could not obtain the mushroom, we showed pictures of possible ones such as *A. smithiana* and *A. proxima* to our patients, and they all pointed out *A. proxima.* Geographically, *A. proxima* is present in Southern Europe [17]. Although it is known that *A. proxima* exists in Turkey, there is only one case of *A. proxima* poisoning reported from Turkey [15].

Mushroom poisoning can lead to some cardiac complications. Case 1 was complicated with acute coronary syndrome, and case 2 had pulmonary edema. Consistent with our cases, the first case of *A. Proxima* poisoning from Turkey was also complicated with cardiac involvement of cardiogenic edema and hypokinetic wall in echocardiography [15]. In another case, cardiac arrest occurred due to A. proxima mushroom poisoning [18]. Apart from *A. proxima*, there are other reported cases of mushroom poisoning and cardiac toxicity [19–21]. Similarly, we think that the cardiac pathologies in our cases are due to A. proxima poisoning.

Treatment of *Amanita* nephrotoxic syndrome consists of supportive treatment and dialysis if required. Knowledge and efficacy of the detoxifying procedures are limited. Besides supportive treatment, silymarin and N-acetylcysteine were used in cases 2 and 3. Because mushroom poisoning was noticed lately in case 1, those were not used. Hemoperfusion was performed for cases 2 and 3, and plasma exchange for case 3. Furthermore, temporary hemodialysis was required in all cases. Kidney injury is expected to resolve entirely in *Amanita* nephrotoxic syndrome, so it is difficult to claim the efficacy of detoxifying procedures. Already, case 1 became independent of dialysis without detoxifying procedures. As expected, all our patients were discharged with renal recovery.

To sum up, although we cannot determine the exact species of causative mushroom, we consider *Amanita* nephrotoxic syndrome in our patients who were all presented with an initial predominant presentation of acute kidney injury. Moreover, we speculated that the causative mushroom should be *A. proxima* with arising symptoms after consecutive consumption the next day and cardiac involvement like the first presented case from Turkey. In conclusion, mushroom consumption must be questioned in acute kidney injury patients of unknown etiology where mushrooms are habitual despite deleterious consequences.

Abbreviations

INR	International normalized ratio
AST	Aspartate aminotransferase
ALT	Alanin aminotransferase
LDH	Lactate dehydrogenase
HCO_3	Bicarbonate
HPF	High power field
HD	Hemodialysis
CVVHDF	Continuous venovenous hemodiafiltration
ANA	Antinuclear antibody
ANCA	Antinuclear cytoplasmic antibody
Anti-GBM	Anti-glomerular basement membrane antibody

Cr	Creatinine
SG	Specific gravity
RBC	Erythrocyte
WBC	Leukocyte
NA	Not available

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MFA and AO drafted the manuscript. AO, AY, and AE reviewed and revised the manuscript. MFA, MS, AO, KÖ, HA, CÖ, EÖK, and FK treated the patients. All authors read and approved the final manuscript.

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Competing interests
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