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## Case Reports
## Acute Renal Failure

# Renal involvement in mushroom poisoning: The case of Orellanus syndrome

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**Abstract**

Although mushroom poisoning is a rare cause of acute renal injury, in some cases it may lead to the development of a severe and irreversible renal failure. Orellanus syndrome is the most important example of organic renal damage related to mushroom consumption. It is caused by the ingestion of orellanine, the main toxin of different types of Cortinarius mushrooms (*Cortinarius speciosissimus*, *C. orellanus*, *C. orellanoides*, etc.), and it is characterized by progressive clinical phases with a predominant kidney involvement, finally requiring renal replacement therapy in about 10% of cases. Renal damage is often late and associated with a histological picture of interstitial nephritis. Diagnosis is essentially clinical and no specific therapy has been shown to be effective in preventing and treating renal damage. Here, we describe the case of a patient with mixed wild mushroom poisoning, presenting the typical clinical signs and course of the Orellanus syndrome. This case offers us the opportunity to review the main clinical features of this severe and little-known intoxication.

**Key words:** Mushroom poisoning, Cortinarius, orellanine, acute kidney injury, hemodialysis

## INTRODUCTION

Toxic injuries are among the main causes of acute renal failure. They may depend on the adverse effects of nephrotoxic substances, such as nonsteroidal anti-inflammatory drugs, antibiotics, and radiological contrast agents, or on direct ingestion of toxins, as in the case of antifreeze.[1–3]

Mushroom poisoning represents a rare cause of toxic renal injury. In spite of the presence of thousands of different species of mushrooms, only few types could be nephrotoxic if eaten.

One of the most important examples of renal damage because of mushroom consumption is the Orellanus syndrome.[4] This syndrome is caused by the ingestion of mushrooms belonging to the Cortinarius species and it is characterized by an early gastrointestinal symptomatology and a transient liver damage, followed by a severe form of acute kidney injury (AKI), leading in some cases to an irreversible end-stage renal disease requiring renal replacement therapy (RRT).[5]

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Here, we report the case of a mushroom poisoning, presenting the typical clinical signs and course of the Orellanus syndrome.

## CASE REPORT

A 77-year-old man was admitted to the emergency department because of nausea, vomiting, and diarrhea. In his history, he presented hypertension, diabetes mellitus type II associated with mild proteinuria (about 800 mg/24 hours) and retinopathy, paroxysmal atrial flutter, peripheral atherosclerosis, and essential thrombocythemia; his renal function was normal with serum creatinine of about 1 mg/dL. The patient was referred for having personally collected and eaten unknown mixed wild mushrooms the day before.

Initial laboratory tests revealed: leukocytosis $30.5 \times 10^9$/L, serum creatinine 2.5 mg/dL, potassium 5.4 mEq/L, glucose 479 mg/dL, Hb 17.1 g/dL, and alanine and glutamic oxaloacetic transaminase (ALT and GOT) 55 and 61 mU/mL, respectively.

Physical examination showed signs of dehydration and basal pulmonary rales, blood pressure was 150/90 mmHg, and chest X-ray showed congested lung fields.

The day after, laboratory examinations showed: ALT 382 mU/mL, GOT 509 mU/mL, amylase 441 mU/mL, and creatinine 3.7 mg/dL. An abdominal ultrasound did not reveal evidence of liver or pancreatic damage. Therefore, in consideration of the recent mushroom ingestion, an empirical therapy with N-acetylcysteine and activated carbon was begun, while his urine was analyzed for detection of amatoxin.

After 48 hours, both liver and renal function further worsened (ALT 3364 mU/mL, GOT 4127 mU/mL, and serum creatinine 5.3 mg/dL), as well as his general clinical conditions. For this reason, the patient was transferred to the intensive care unit. Meanwhile, the research of amatoxin resulted positive and therapy with cathartics and activated carbon was enhanced.

Three days after (i.e., the sixth day after mushroom ingestion), while liver tests and general conditions were slightly improving, the patient presented a further significant increase in serum creatinine levels (up to 7.9 mg/dL) associated with an abrupt onset of oliguria (100 mL/24 hours), requiring the prompt initiation of hemodialysis (Figure 1).

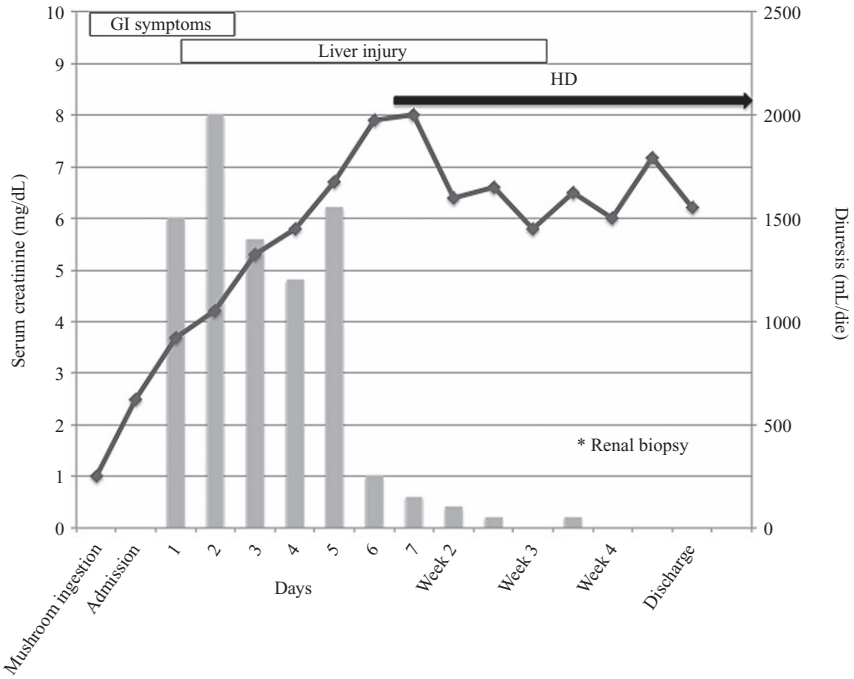


**Figure 1** The patient's clinical course after mushroom ingestion. The patient initially presented a gastrointestinal (GI) symptomatology, then he developed liver and kidney injury. Serum creatinine (gray line) progressively increased, while diuresis (columns) dramatically decreased starting from the sixth day after the admission, when hemodialysis (HD) began. At the discharge, patient's general conditions were good, but he still required regular HD.

In the following days, transaminase levels decreased and the hemodynamic remained stable, while renal damage persisted until the patient became anuric.

Then, he was transferred to our Nephrology Unit. After optimizing the extracellular volume status and reviewing the pharmacological therapy, as renal function did not improve and AKI etiology remained unknown, a renal biopsy was performed (on the 25th day after mushroom ingestion).

Light microscopy showed obsolescence of three glomeruli, while other glomeruli presented different degrees of mesangial matrix expansion and thickening of glomerular basement membrane. Tubular atrophy and some tubular cast were also present, associated with moderate sclerosis and interstitial lymphocytic infiltrate (Figure 2). Staining for immunoglobulins and complement was negative.

This histological picture was considered suggestive for an acute interstitial nephritis superimposed on chronic renal damage. Due to the anamnestic data of recent mushroom ingestion and patient's clinical course, a diagnosis of Orellanus syndrome was suspected.

Therefore, the patient was treated with oral corticosteroids at the dose of 1 mg/kg/die orally for the first 2 weeks, then tapered and stopped after 6 weeks, as he remained anuric and developed side effects of steroid therapy.

Later on, the patient's renal function did not recover and, 12 months after the first admission, the patient's clinical conditions were good, but he still continued regular intermittent hemodialysis.

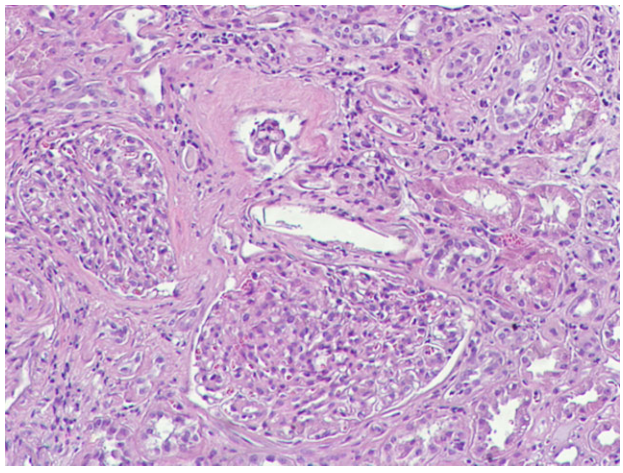

**Figure 2** Renal biopsy performed at the 25th day after mushroom ingestion. The biopsy showed features of chronic damage, such as mesangial matrix expansion, thickening of the glomerular basement membrane and tubular atrophy, associated with moderate interstitial lymphocytic infiltrate (hematoxylin-eosin, magnification ×100).

## DISCUSSION

Here, we present a case of acute and irreversible renal injury highly consistent with Orellanus syndrome because of the history of mushroom ingestion and the clinical course.

Orellanus syndrome, caused by the ingestion of orellanine, the main toxin of different types of Cortinarius mushrooms (*Cortinarius speciosissimus*, *C. orellanus*, *C. orellanoides*, etc.), is characterized by a delayed acute tubulopathy that can progress toward chronic renal failure.

Clinical experiences, as well as experimental data, indicate that there is a considerable individual difference in susceptibility to the toxin, which reasons remain still unknown.[6]

Orellanus syndrome usually starts with a latent phase (which can vary from 12 hours to 14 days, with a median of 3 days), followed by a pre-renal phase, with systemic and gastrointestinal symptoms (nausea, vomiting, and diarrhea), and an oliguric renal phase. The renal phase of the poisoning can appear while the gastrointestinal symptoms are still present, usually after a period of 3 days up to 17 days. Out of 70% of the cases, renal damage progresses toward chronic renal failure, which justifies RRT in 10–50% of the cases.[7–9]

The mechanisms of the orellanine-mediated nephrotoxicity remain unclear. Orellanine is a tetrahydroxylated di-N-oxidized bipyridine that, in vitro, directly inhibits the synthesis of proteins, RNA, and DNA in tubular cells.[10] Moreover, it might promote oxidative cell damage through the generation of an ortho-semiquinone radical, which depletes glutathione.[11,12]

Diagnosis of Orellanus syndrome is prevalently clinical, based on patient history and clinical course, as orellanine toxin results undetectable in plasma and urine.

In most cases, renal biopsy shows a picture of predominant interstitial nephritis with a progressive interstitial fibrosis, while glomerular lesions are generally absent.[13] The biopsy of our patient differed from this classical picture, mainly because of the presence of chronic glomerular lesions, a finding probably due to his past history of diabetes, hypertension, and renal dysfunction.

When there are no mushroom samples available, as in our case, direct detection of orellanine in renal biopsy tissue using a thin-layer chromatography has been described, but this technique is not widely available.[14]

Notably, Cortinarius poisoning must be separated from the less known "Amanita nephrotoxic syndrome," characterized by an early onset of gastrointestinal symptoms, mild hepatic damage, and severe but reversible AKI.[15]

Considering the overall history and clinical course of our patient, our hypothesis is that in this case the impairment of renal function was due to the coexistence of different conditions, related to a mixed mushroom poisoning. In particular, in the early phases, AKI was probably secondary to extracellular volume depletion and Amanita nephrotoxicity, while later Orellanus syndrome occurred, which was responsible for the definitive loss of patient renal function.

There is no specific therapy for Orellanus syndrome and, hence, treatment is mainly supportive. Different attempts have been made with plasma exchange, early hemodialysis, corticosteroids, and N-acetylcysteine.[16,17] In particular, N-acetylcysteine, in association with corticosteroids and selenium presented encouraging results in isolated cases, but none of these interventions was able to prevent chronic renal damage.[18] It is possible that the lack of efficacy of all these therapies may be due to the fact that the toxin is quickly cleaved from the plasma, whereas it is highly concentrated in the renal tissues.

Finally, there are concerns about the opportunity of renal transplantation in patients with Orellanus syndrome, mainly because of the potential harm to the graft from the toxin released from native kidneys. However, this event has never been described until now and some cases of successful renal transplant after Orellanus syndrome have been reported, so the chance of renal transplant should not be denied to these patients.[19,20]

In conclusion, we report an illustrative case of rare but severe form of acute kidney injury secondary to mushroom poisoning. This case highlights the importance to spread knowledge about the potential nephrotoxicity of mushrooms, suggesting that in cases of AKI of unknown origin, the ingestion of mushrooms of the Cortinarius species should be included in the differential diagnoses.

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