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Clinical Report

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High-dose antioxidant therapy and steroids might improve the outcome of acute renal failure from intoxication by *Cortinarius rubellus*: report of two cases

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Abstract
Only a small number of cases with favourable outcome after acute renal failure due to intoxication by *Cortinarius* sp. have been reported in the literature, and approximately half of the patients develop chronic renal failure and dialysis-dependency. We report the case of a couple with acute renal failure after accidental intake of *Cortinarius rubellus* and a favourable outcome after treatment with high-dose antioxidant therapy with *N*-acetylcysteine and steroids. Dialysis was never necessary in both patients and renal function was almost normal at the end of follow-up. Underdiagnosis of this rare cause of acute renal failure is likely due to the fact that affected patients develop symptoms of intoxication after a delay of 2–30 days. In patients with unclear acute renal failure with or without gastrointestinal symptoms, intoxication from *Cortinarius* sp. should be considered as a differential diagnosis. Early treatment with high-dose antioxidant therapy and steroids might be effective in reducing the risk of chronic renal failure.

Keywords: acute renal failure; *Cortinarius rubellus*; intoxication; therapy

Background

Acute renal failure following intoxication by mushrooms of the *Cortinarius* sp. has been described sporadically. Since the first reports were published in 1957 in Poland [1], only a small number of cases with favourable outcome has been reported in the literature [2, 3], whereas approximately half of the patients with acute renal failure from intoxication by *Cortinarius* sp. developed dialysis-dependent chronic renal failure. Treatment strategies include symptomatic treatment, haemodialysis, plasmapheresis, steroids and *N*-acetylcysteine [2–6, 7]. We report the case of a couple with acute renal failure after accidental intake of *Cortinarius rubellus* and an almost complete recovery after treatment with high-dose *N*-acetylcysteine, an antioxidant, and steroids.

Case report

A 62-year-old woman was transferred to our nephrology unit from a peripheral hospital due to acute renal failure of unknown origin. Four days before admission she complained of nausea, vomiting and an epigastric feeling of pressure. The patient denied any recent consumption of nephrotoxic drugs. However, two days prior to the onset of symptoms she and her husband had picked, cooked and eaten wild mushrooms, which she had taken for mushrooms called *Cantharellus cibarius*. Both of them were rather inexperienced in mushroom picking. Immediately, the husband was informed about the suspected diagnosis of mushroom poisoning. On pictures shown to them, they positively identified a *Cortinarius* sp., which they had taken for chanterelles (*Cantharellus cibarius)*. In the female patient, a physical examination showed an elevated blood pressure of 160/77 mmHg, a body temperature of 37.5°C and a pulse rate of 52. The patient was in a reduced general condition and had epigastric pain. Laboratory tests revealed anaemia (haemoglobin 11.5 g/dL), serum creatinine of 587.0 µmol/L (6.64 mg/dL) and urea of 28.2 mmol/L (169.5 mg/dL). Levels of potassium, chloride and phosphate were also increased. In addition, laboratory tests showed the following liver function parameters: glutamate oxaloacetate transaminase 65 U/L, glutamate pyruvate transaminase 61 U/L and gamma-glutamyl transferase 74 U/L. The protein-to-creatinine ratio in urine was 0.59 mg/g. Immunological parameters and virological tests were all negative. A renal ultrasound showed no specific abnormalities and the kidneys were of normal size. A renal biopsy was performed 2 days after admission. Histological examination by light microscopy showed acute interstitial nephritis of lymphomononuclear type and globally preserved glomeruli (Figure 1). Higher magnification of the tubulointerstitium revealed tubular dystrophy with anisometric vacuolization, loss of brush border membranes and debris in the tubular lumina. There could be seen a moderate acute tubular damage and minimal acute non-destructive tubulointerstitial nephritis, probably

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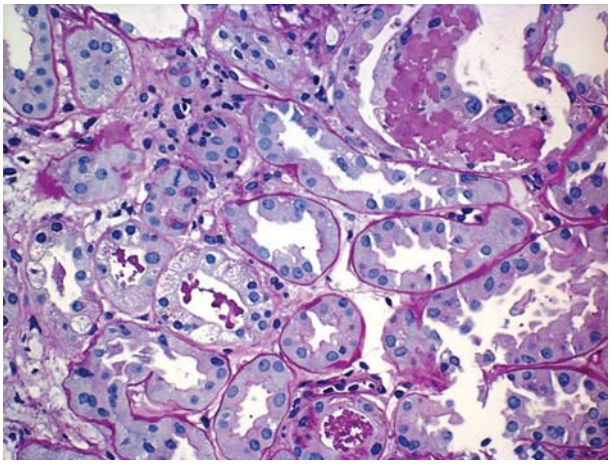

Fig. 1. Kidney biopsy specimen in light microscopy (PAS). Glomeruli (not shown) were normal.

Fig. 2. *Cortinarius rubellus*.

due to orellanus toxicity. Thin-layer chromatography of a properly processed biopsy specimen as previously described failed to detect the toxin orellanin.

The patient's husband was immediately informed after his wife's hospital admission. He complained of mild nausea for 4 days, but he had had no vomiting. A physical examination showed an elevated blood pressure of 154/73 mmHg, a body temperature of 37.4°C and a pulse rate of 62. Laboratory tests revealed serum creatinine of 890.2 µmol/L (10.07 mg/dL) and urea of 36.8 mmol/L (221.1 mg/dL). The level of potassium was 5.2 mmol/L, the phosphate level was increased and the calcium level was decreased. Liver function parameters were in the normal range. Urinalysis showed microhaematuria, and the protein: creatinine ratio was 0.11 mg/g. At ultrasonography imaging, the right kidney showed broadened renal parenchyma, and the resistance index was increased in both the kidneys. No renal biopsy was performed.

Both patients were started on prednisolone 1 mg/kg once daily and treated with intravenous *N*-acetylcysteine in the dosage used for intoxication with paracetamol (150 mg/kg over 15 min, followed by 50 mg/kg over 4 h and 100 mg/kg over 16 h). Renal function of both patients improved significantly over the course of the next 8 days and they were discharged from the hospital on a reducing course of prednisolone. After that, a meeting between the two patients and the biologist who had carried out the toxin analysis of the renal biopsy specimen was undertaken, which revealed that with the utmost probability the causative mushroom was *C. rubellus* (Figure 2) which is rather common in this part of Tyrol.

After 59 days, the serum creatinine of the female patient was 110.5 µmol/L (1.25 mg/dL), and was 136.1 µmol/L (1.54 mg/dL) for the male patient. We then repeated antioxidant therapy with *N*-acetylcysteine in the same dosage as on Day 1 and the female patient had to be started on antihypertensive medication. Prescription of prednisolone was stopped 103 days after intoxication. A recent examination 306 days after intoxication showed stable values of creatinine in both patients.

Discussion

Although reports from Austria of acute renal failure due to intoxication by *Cortinarius* sp. are rare [2], mistaking this mushroom as *Cantharellus cibarius* and others like *Arimillaria mellea* and *Psilocybe sp.* is well described and probably occurs more often than reported since *Cortinarius* sp. can be found all over Europe and North America. Underdiagnosis of this rare cause of acute renal failure is likely due to the fact that affected patients develop symptoms of intoxication after a delay of 2–30 days. In our case, the female patient had symptoms as early as 2 days after ingestion of a meal containing self-picked mushrooms. It is not uncommon that detection of the toxin in biopsy specimens fails [4, 5], so clinical circumstances and the result of the kidney biopsy showing interstitial nephritis without other pathological findings make other causes of acute renal failure very unlikely.

Nephrotoxicity of *C. rubellus* has been found to be due to toxine orellanin [8], a tetrahydroxylated di-*N*-oxidized bipyridine, which is rapidly concentrated in the kidneys. It has been shown *in vitro* that the oxidation of orellanine by biological oxidizing agents leads to the production of an anion radical and reactive oxygen species following oxygen consumption and depletion of glutathione. It seems reasonable to hypothesize that antioxidant therapy such as *N*-acetylcysteine, acting as a glutathione donor, might reduce the extent of nephrotoxicity through reducing oxidative stress.

Based on these pathophysiological considerations and in view of the grim prognosis of dialysis dependency in ∼50% of patients with orellanin intoxication, we decided to start steroids and *N*-acetylcystein.

Since Gryzmala [1] reported in 1957 that corticosteroids did not influence the progression of renal insufficiency after intoxication with *Cortinarius* sp., only a few authors reported that they had given steroids to their patients. However, as ingestion of *Cortinarius* sp. almost always causes severe interstitial nephritis, addition of steroids to symptomatical and antioxidant treatment should be considered [9]. Kilner *et al.* [3] reported the case of a patient with acute renal failure due to ingestion of *Cortinarius* sp., who initially had to undergo dialysis and was successfully treated with prednisolone 60 mg per day and *N*-acetylcysteine once in the dosage mentioned above leading to renal recovery after 2 months.

It has been proposed [2] that early plasma exchange after ingestion of *Cortinarius* sp. might reduce renal toxicity.

However, Montoli *et al*. [7] reported the case of a patient, who developed chronic renal failure despite a complete plasma volume exchange 44 h after ingestion of these mushrooms. In the same manner, benefit of early haemodialysis treatment remains unclear. Horn *et al*. [2] hypothesized that the chance of renal recovery depends on the amount of ingested toxin, age and general health of the individual patient, and the delay until the therapy is started.

In conclusion, in patients with acute renal failure with or without gastrointestinal symptoms intoxication by *Cortinarius* sp. should be considered as a differential diagnosis, especially in those regions where picking wild mushrooms is very popular. Early treatment with antioxidant therapy and steroids might be effective in reducing the risk of developing end-stage renal failure.

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Conflict of interest statement. None declared.

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