Acute kidney injury related to wild mushrooms intoxication

Running title: Mushroom intoxication related acute kidney injury

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Abstract:
The problem of mushroom intoxication has been brought up more often in both scientific journals and media, particularly in autumn – the period when mushroom hunting is most intense. Mushroom intoxication is mainly perceived as being associated with acute hepatic insufficiency. However, apart from strong hepatotoxic effects, some mushroom species are characterized by effects that lead to renal damage, sometimes irreversible in character. This article relates to the toxic mushroom species considered to be nephrotoxic and discusses different mechanisms and symptoms of kidney injury as well as methods of treatment.

Keywords: Wild mushroom intoxication, Nephrotoxicity, Kidney insufficiency, Orellanine nephrotoxicity, Amatoxin nephrotoxicity, Paxillus syndrome

Article:
In recent years, the problem of mushroom intoxication has been brought up more often in both scientific journals and media, particularly in autumn – the period when mushroom hunting is most intense. According to the National Institute of Hygiene of Poland there is a downward trend in the incidence of mushroom intoxication, resulting mainly from a higher public awareness. A disturbing fact is an increased interest in hallucinogenic effects of mushroom among young people [1]. Mushroom intoxication is mainly perceived as being associated with acute hepatic insufficiency. However, apart from strong hepatotoxic effects, some mushroom species are characterized by effects that lead to renal damage, sometimes irreversible in character. This article relates to the toxic mushroom species considered to be nephrotoxic.

The subject of toxic properties of species of the Fungi kingdom was studied in 1950s by Stanislaw Grzymała who isolated orellanine – a hit-stable substance responsible for renal damage [2]. He also presented case reports on orellanine intoxication. In 1957 Grzymała reported the first incidence of acute intoxication after ingestion of Cortinarius orellanus in Bydgoszcz in Poland. About 100 inhabitants developed acute kidney failure after an ingestion of this mushroom. The mortality was over 10%.

Orellanine is an alkaloid that is insoluble in water. The substance is thermostable, i.e. it does not undergo degradation upon boiling or frying. Orellanine chemically resembles pyridine herbicides paraquat and diquat and deoxidizes in ultraviolet light to a non toxic metabolite – orelline [3, 4, 5]. Nephrotoxic activity of orellanine mostly occurs through selective damage to renal tubule cells, which leads to necrotic and degenerative lesions. However, the exact mechanism behind orellanine nephrotoxicity has not yet been explained [6]. Renal biopsy in affected patients reveals interstitial glomerular damage [4, 7, 8]. Orellanine causes severe non glomerular renal injury by an unknown mechanism [7, 9]. Clinically the patients presents anorexia, headache, nausea, vomiting, diarrhea, flank pain. The initial symptoms may be easily overlooked as the first symptoms begin 36 to 48 hours post ingestion [7, 10]. Serious toxicity does not occur for several days [11, 12]. The nephrotoxin causes an irreversible renal failure in severe cases (orellanus syndrome). Acute kidney injury (AKI) occurs only in 30-50% of cases [10, 12, 13]. Due to dilate presentation, a clinician must consider orellanine toxicity in any patient with an unexplained AKI. Damage to the kidneys can be confirmed by thin layer chromatography of renal biopsy specimens or by plasma assays for orellanine and orellin [14, 15, 16]. Due to an accumulative properties ingestion of small yet repeated doses of orellanine can lead to fibrosis and acute tubular necrosis.

An example of species containing orellanine is fool’s webcap, Cortinarius orellanus, which may be fatal when ingested even in small quantities (~150g). Intoxication with Cortinarius orellanus is characterized by a relatively late onset of full symptoms which may develop as late as after several days. The only treatment that may be applied at the time of the onset of
symptoms is hemodialysis as a temporary support until an adequate renal function returns, and finally a renal transplant [17]. A successful case of living donor kidney transplantation to a patient with kidney insufficiency related to Cortinarius orellanus intoxication after 20 months haemodialysis treatment has been recently described [18]. The efficacy of the treatment with N-acetylcysteine and corticosteroids reported by Kilner [6] was not confirmed in another study [19].

Orellanine was recently also found in a mushroom Cortinarius armilatus with HPLC (high-performance liquid chromatography) and LC-MSMSL (liquid chromatography-tandem mass spectrometry) [20]. Another popular mushroom-related nephrotoxin is an amatoxin. The amatoxin containing species of mushrooms, which is the most common of its critical intoxication, is Amanita phalloides and it is responsible for over 90% of fatalities worldwide. The most notorious for intoxication incidence is death cap (Amanita phalloides), that similarly to the well-known destroying angel (Amanita virosa), contains hepatotoxic cyclopeptides which, when ingested, lead to fulminant hepatic failure and multiple organ dysfunction referred to as Phalloides syndrome. A particular danger with this intoxication lies in the fact that the symptoms may develop as late as after 24 hours when, in most cases, the liver has become completely insufficient. The genus Amanita includes also two other species, i.e. Amanita smithiana and Amanita proxima, which has been described as nephrotoxic in numerous reports [11, 21]. A. smithiana occurs mostly on the west US coast (California), while A. proxima grows in the Mediterranean Basin. Intoxications with A. smithana are due to its high similarity to edible species, particularly matsutake (Tricholoma magnivelare), which is much valued by culinary connoisseurs with price reaching USD 2000/kg. Other species of the genus were also subjected to toxicity tests. The toxin responsible for renal damage was detected also in A. boudieri (Portugal), A. gracilior (Portugal), A. echinocephala (Germany) [22]. Symptoms of intoxication with Amanita mushrooms include mainly gastrointestinal disorders with a quite early onset of about 6 hours. Most studies demonstrate increases in aminotransferase levels which may occur between the first and the fifth day after ingestion. Renal failure develops over 3-5 days in contrast to nephrotoxic orellanine containing ingestions. Chronic renal disease and stage V chronic renal failure occurs in as many as 51% of patients. Renal function recovery in Amanita intoxication is estimated at 100% [12].

Another species responsible for an acute renal damage is Paxillus involutus. It exerts nephrotoxic effect in an indirect mechanism. Ingestion of the mushroom leads to antigenic stimulation and secretion of IgG antibodies followed by development of immune complexes, which bind to the erythrocyte membranes and lead to a massive hemolysis, hemoglobinuria and renal damage. The symptoms are referred to as the Paxillus syndrome. Since the symptoms originate from the activity of immune complexes, plasmapheresis has been used successfully in the treatment of the syndrome [23].

Renal damage secondary to mushroom consumption may also be due to ingestion of yellow knight - Tricholoma equestre. Nephrotoxic properties of the mushroom entails the development of rhabdomyolysis – a process of myoglobin permeation from damaged muscles into the blood. This may lead to a necrosis of renal tubules. Main clinical symptoms include muscle weakness, fatigue, myalgia, erythema, nausea without vomiting. The symptoms develop within 24-72 hours. Deviations in laboratory investigations include significant elevation in creatine phosphokinase (CPK) levels [22]. In one of the reported cases, concentration of CPK following ingestion of Tricholoma equestre was 44767 U/L. Another report was a case of a patient who died due to respiratory failure caused by a strong intoxication with Tricholoma equestre despite an extensive treatment [24].
Poisoning with fungus Russula subnigricans is another cause of rhabdomyolysis, which can be classified as a late onset rhabdomyolysis. Such case, which led to rhabdomyolysis, acute kidney injury, renal failure, cardiac arrhythmias and patient’s death was described in South Korea [25].

Studies of toxins contained in various mushroom species are ongoing and one may suspect that there is a considerable number of potentially life-threatening substances that have not been described to date. Mechanisms leading to renal damage caused by these mushrooms have not been fully elucidated and require a continued monitoring.

So far there is no specific treatment for mushroom poisoning and attempts of application of N-acetylcysteine and GKS were not successful [19]. Thus, one should exercise particular care when hunting for mushrooms and be sure to eat only the species that one is 100% certain are edible.

References