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Acute renal failure following collective intoxication by *Cortinarius orellanus*

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Abstract. Twenty-six young men with no previous medical history all ingested mushroom soup, exclusively made with *Cortinarius orellanus*. They were hospitalized 10–12 days after the incident. On admission, 12 patients presented with acute tubulointerstitial nephritis with acute renal failure; 8 required haemodialysis. In addition to symptomatic treatment, 9 patients were given corticosteroids. In this group of 12 patients, 8 recovered rapidly, and the other 4 suffered from chronic renal failure for several months. In the other group of 14 patients, initial leukocyturia was observed in 12 cases, although renal function remained normal during a one-year follow-up. Hepatic acetylation and hydroxylation tests performed after 6 months in 22 patients did not provide any explanation for the strong individual sensitivity to the renal toxicity of this fungus.

Key words: Acute renal failure – Mushroom poisoning – *Cortinarius orellanus*

Since the clinical study of 135 cases of poisoning with *Cortinarius orellanus*-type mushrooms reported in 1965, which were responsible for 19 deaths secondary to acute renal failure [1], several isolated cases have confirmed the severity of the renal involvement that follows ingestion of various types of *Cortinarii orellanus* [2–6], *speciosissimus* [7–10] and *splendens* [11]. When present, this renal failure is severe, often oliguric, and improves within a few weeks in 50%–70% of cases; in other cases, renal failure persists and requires chronic haemodialysis for several months or even years.

We report here a case of accidental collective poisoning following ingestion of *Cortinarius orellanus* in 26 young men with no previous medical history. The renal consequences of this intoxication were assessed over a one-year follow-up period.

Patients and methods

During a survival exercise in September 1987, 26 soldiers aged 21–28 (mean 24.7 years) ate in quite identical quantity a mushroom soup made exclusively with *Cortinarius orellanus*. This mushroom was later found on location and was identified by them as well as by a mycologist. Up to the 10th to 12th day following ingestion, trivial symptoms were recorded that did not preclude intensive physical activity for 25 of them. Past that time, all were hospitalized for some time and regularly followed-up for one year. Six months after the incident, acetylation and hydroxylation hepatic functions were studied using the isoniazid test [12] and the debrisoquine test [13] respectively in the 22 patients whose renal function was normal.

Two groups of patients were defined, according to the existence or not of initial renal failure: Group 1 ($n = 12$): blood creatinine >150 µmol/l, Group 2 ($n = 14$): blood creatinine ≤ 150 µmol/l.

The biological values of each group were expressed as means ± SD. Statistical analysis was performed using the χ^2 test with Yates' adjustment for comparison of qualitative data, and the Mann-Whitney test for comparison of quantitative values.

Results

Table 1 shows the initial symptoms presented by all 26 patients between ingestion and hospitalization; these signs occurred between the 2nd and 4th days following ingestion in Group 1, and between the 3rd and 9th days in Group 2.

Group 1: Upon admission to hospital (11th day on average), 8 patients complained of lumbar pain, 4 of paraesthesiae in the extremities and dysgeusia and 3 of skin rash. The initial clinical data and the treatments that were implemented are reported in Table 2. Mean serum creatinine in this group was 1293 ± 733 µmol/l; 4 patients were anuric. Haemodialysis was necessary on the day of admission in 8 cases. Leukocyturia (mean 54200 ± 33600 leukocytes/ml) was marked in the 7 patients where it was investigated, associated with microscopic haematuria (mean 18100 ± 12700 RBC/ml). Gallium scintigraphy, performed in 5 patients, revealed elevated and homoge-

Table 1. Clinical signs occurring between ingestion and hospitalization in both patient groups

	Group 1 $n = 12$	Group 2 $n = 14$	χ^2 test with Yates adjustment
Digestive disorders	12	3	$p<0.001$
Asthenia	7	0	$p<0.01$
Thirst	9	5	$p<0.05$
Headache	6	1	$p<0.05$
Chills	5	0	$p<0.05$
Polyuria	5	3	NS

neous bilateral renal fixation of the tracer (renal/hepatic fixation index = 0.89±0.37; renal fixation/dose ratio = 15.4%±4%).

Renal histology performed in 7 patients revealed tubulointerstitial lesions in all of them: these lesions were characterized by a loose, inflammatory edema (Fig. 1) with infiltrates that included either polynuclear cells, with no eosinophils, or mononuclear cells, lymphocytes and histocytes, the latter proliferating in place of tubulorrhexis tubes. There were acute tubular lesions with epithelial necrosis, and proteic and granular cylinders. Immunological study of the inflammatory cells (monoclonal antibodies) revealed the presence of B lymphocytes. The glomeruli and vessels were normal. Immunofluorescence did not reveal any significant binding of immune deposits. In addition to iterative haemodialysis, corticosteroid treatment was initiated between the 11th and the 19th days following ingestion in 9 patients (re. Table 2): intravenous bolus injection of 10 mg/kg/day methylprednisolone for 3 days, followed by 1 mg/kg/day prednisone for 3 weeks. The evolution of blood creatinine over one year (Fig. 2) showed that 8 patients rapidly recovered normal renal function (mean serum creatinine at 1 month = 137.6±46 µmol/l; at 3 months = 108±30; at one year = 110±28). Renal failure persisted in 2 patients under sustained diuresis (cases 2 and 3), one patient was successfully transplanted after 10 months (case 12), one patient has remained under chronic haemodialysis (case 5); a second renal biopsy performed in this patient at 3 months showed a recession of the interstitial lesions, but persistently evolving tubular lesions (Fig. 3). Germ-free leukocyturia was found in 3 cases at 3 months, and in 5 cases at 2 months.

Eosinophilia was below 400/mm^3 during the first two days of hospitalization; it was transiently up to 1000/mm^3 in one patient who had a skin rash upon admission. Serum complement titration performed in 6 patients was normal: total complement = 45.4±13.3 g/l ($n = 46\pm12$), C_3 fraction = 1.15±0.28 g/l ($n = 1.38\pm0.45$), C_4 fraction = 0.25±0.06 g/l ($n = 0.29\pm0.16$). None of the patients had circulating immune complexes.

Group 2: Clinical examination of these patients upon admission did not reveal any abnormality. Mean blood creatinine was 97.8±10 µmol/l. Marked leukocyturia (mean 35900±34000 leukocytes/ml) was found in 12 cases, associated with microscopic haematuria in 3 patients. No renal scintigraphic or histological exploration was performed. No treatment was prescribed. Renal function remained normal throughout: mean serum creatinine = 95.2±8 µmol/l at 1 month, 87.2±8 at 3 months, and 91.6±8 after one year. Leukocyturia was still present after one month in 10 patients.

No other abnormality was detected in these 26 patients: hepatic tests were and remained normal. One hepatic biopsy (case 12) was normal.

In the 22 patients with normal renal function (8 from Group 1, 14 from Group 2), acetylation (inactivation index = 0.334±0.5 in Group 1; 0.358±0.8 in Group 2) and hydroxylation phenotypes (metabolic ratio = 1.39±0.5 in Group 1, 0.87±0.9 in Group 2) were not significantly different.

Table 2. Clinical data upon hospitalization and treatments applied to Group 1 patients

Case no.	Days from ingestion to admission	Clinical data upon admission				Methods and treatments			
		Serum creatinine µmol/l	Diuresis l/24 h	Leukocyturia C/ml	Haematuria C/ml	Gallium scintigraphy	Renal biopsy	Dialysis	Days from ingestion to steroid therapy
1	11	1176	2.5	44400	11000	●	+	+	13
2	10	2076	0	–	–	+	+	+	11
3	11	1989	0	–	–	+	+	+	11
4	11	376	4.3	15100	<1000	●	●	–	–
5	11	1980	0	–	–	+	+	+	17
6	11	848	3	88800	<1000	●	●	–	–
7	11	1780	2.2	5327	7850	+	+	+	17
8	11	1240	0	–	–	+	+	+	11
9	11	172	2.2	26600	<1000	●	●	–	–
10	11	352	1.7	124400	<1000	●	●	–	19
11	11	1280	2.0	75100	17300	●	●	+	13
12	13	2248	0.6	–	–	●	+	+	17

C/ml = Count/ml; l/24 h = l/24 h

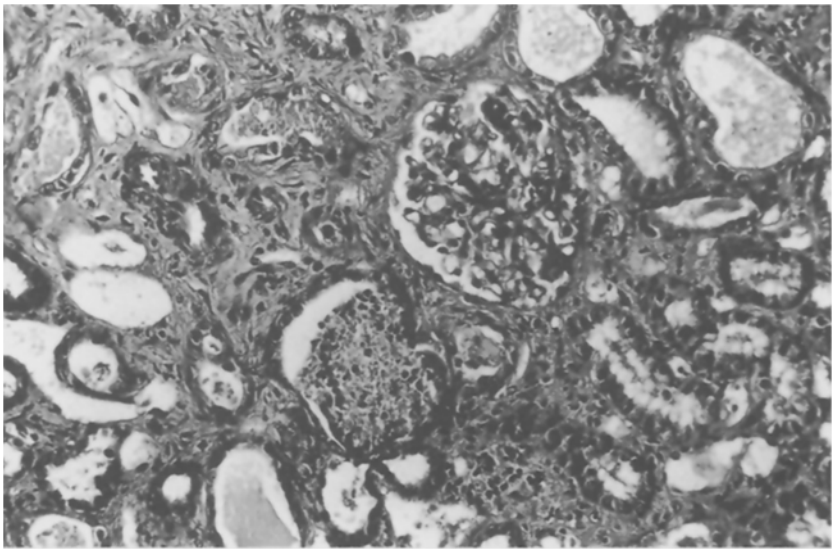

Fig. 1. Renal biopsy: Acute degenerative tubular lesions with inflammatory interstitial fibrosis (Masson's trichrome X 80)

Discussion

Cortinarius orellanus is a brown-coloured, slightly orange-shaded mushroom, rather ubiquitously found in Europe, at the end of summer or in autumn in semi-mountainous woodlands, more rarely in plains.

The responsibility of this fungus species in the collective poisoning reported here cannot be questioned: exclusive ingestion, identification on location, and confirmation by a mycologist. All patients ate the same quantity of mushroom soup, as confirmed by the presence of clinical signs in both groups.

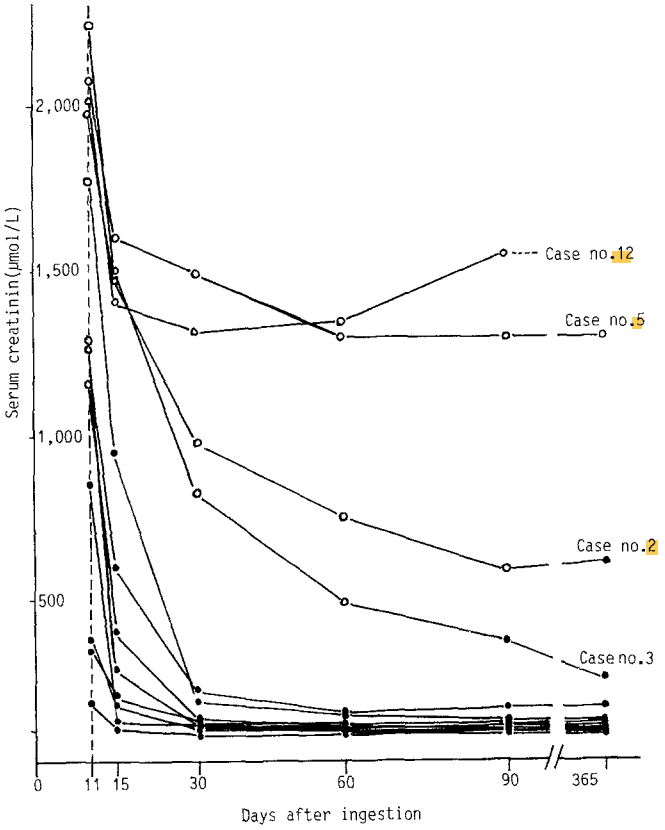

Fig. 2. Evolution of blood creatinine in Group 1 patients over one year (○ with haemodialysis; ● without haemodialysis)

The peculiar clinical pattern is common to several types of *Cortinarii* (*orellanus*, *speciosissimus* and *splendens*). The first specific characteristic of this poisoning is the latency period between ingestion and the first clinical signs: these occur 2 to 3 days following ingestion, sometimes as long as 20 days [14]. Non-specific digestive signs (abdominal pain, nausea, vomiting, diarrhoea in some cases) precede the deterioration of the patients' general condition, with thirst, chills, headache, polyuria. As observed, these signs occur earlier and with higher frequency and intensity in the patients who later develop renal failure. As previously reported, wide variations in individual sensitivity account for the lack of correlation between the amount ingested and the intensity of these signs [11, 14]. Clinical signs may spontaneously disappear in some patients, leaving the poisoning unnoticed; in others, the signs become more intense and are accompanied by neurological manifestations (paraesthesia, taste impairment, sometimes cognitive disorders), lumbar pain, and sometimes anuria requiring hospitalization.

Renal involvement is the other peculiarity of this poisoning, which makes it so serious. Its detection is delayed, sometimes until the 15th day following ingestion, which accounts for the etiological problems encountered when mushroom ingestion has remained ignored. Routine examination of our patients showed that renal failure is not systematic: 12 patients from group 2 presented with marked leukocyturia, sometimes associated with microscopic haematuria, possibly reflecting an underlying interstitial nephritis. In the most severe cases, renal involvement led to variably severe renal failure, sometimes with oliguria. In the Polish epidemiological study and the rare cases of collective poisoning reported, the incidence of renal failure varies from 30% [1] to 35% [11]; it was 46% in our study. The renal histological lesions that we found are consistent with both clinical and experimental obser-

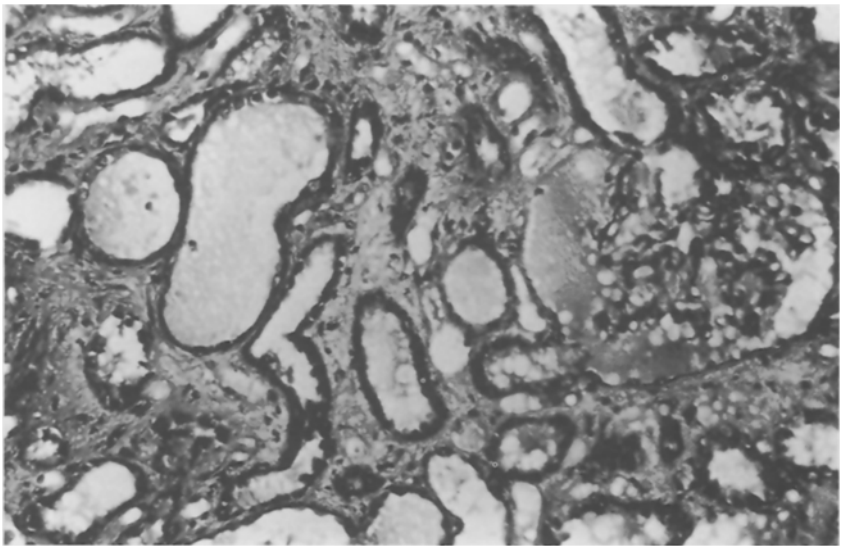

Fig. 3. Renal biopsy 3 months after poisoning: loose, mildly inflammatory fibrosis with degenerative tubular lesions (Masson's trichrome X 80)

vations [15]: the extent of tubular lesions with epithelial necrosis (persisting for at least 3 months), and disruption of the tubular basement membrane leading to the formation of granulomata suggest a direct toxic mechanism of this acute nephritis. The absence of eosinophilia and the normal serum complement range would be additional insights for a toxic rather than an immuno-allergic mechanism. The extensive renal binding of gallium in scintigraphy, which is the reflection of the interstitial involvement, may provide an evolutionary approach to renal disease [16]. Compiling the clinical cases of poisoning by the various *Cortinarius* species makes it possible to distinguish two types of evolutionary patterns of renal failure: with *Cortinarius orellanus*, recovery (with or without symptomatic treatment) was obtained within an average period of one month in 66% of cases in our study, compared to 64% in other reports [2–6]; it has been reported to be 46% with *Cortinarius speciosissimus* [7–10], and 67% with *Cortinarius splendens* [11]. In all other cases, renal failure persisted and most often required iterative haemodialysis. The oliguria observed on admission would appear, in our experience, to be a factor of pejorative renal outcome (cases 2, 3, 5 and 12). However, the one-year follow-up showed that a slow and progressive recession of renal involvement is possible.

The kidneys seem to be the only organs to be affected by such poisoning: in our study, no hepatic affection was detected, in confirmation of experimental studies [15]; the hepatic biological disorders reported by some investigators [4] may be explained by the difficulty to identify a posteriori the mushroom involved, and concomitant ingestion of other species.

Experimental studies made it possible to isolate, from the various types of *Cortinarii*, two main toxins: Orenalline and Cortinarines [17–19]. Even if the respective involvement of these two toxins is still controversial, they do reproduce, in animal experimentation, renal lesions similar to those observed in man after severe poisoning, with similar latency periods [15]. Recently, orenalline could be evidenced in a renal biopsy specimen 13 days after voluntary poisoning [3]. The exact mechanism of toxicity has yet to be elucidated: the latency period between ingestion and the occurrence of the first clinical signs, the sexual variations observed experimentally [20] and the great individual sensitivity reported by some authors [1, 11] and observed in our study, would suggest that renal toxicity may result from the toxin(s) hepatic metabolism. The homogeneity of the results from the acetylation test and those from the debrisoquine test, evaluating the hydroxylation capacity of hepatic P450 cytochromes, did not provide any explanation for the strong individual response to the renal toxicity of this fungus.

Therapeutic prospects result from experimental data and clinical observations. As for drug-induced tubulointerstitial nephritis, we gave corticosteroid treatment to 9 patients, due to the severity of their renal inflammatory lesions [21]: this treatment did not alter the evolution of renal failure, probably because it was initiated too late. Even if the toxin could be detected in the blood for at least 10 days after poisoning [22], its early and irreversible renal fixation and the absence of any renal prognostic criteria make extracorporeal techniques irrelevant and useless: few reported cases have used plasma exchange [7] or haemoperfusion with charcoal filter or Amberlite resin [8, 23]; they did not yield any change in the evolution of renal involvement. In fact, during severe poisoning with renal failure, the only adapted treatment is symptomatic: haemodialysis, which in addition may eliminate the free circulating toxin still present because of its low molecular weight; furosemide seems to aggravate renal lesions [24].

Conclusion

The severity of *Cortinarius orellanus* poisoning is linked to acute renal failure. The latency of clinical signs in relation to ingestion, and the high individual sensitivity are two typical characteristics of this poisoning. Renal failure disappears within one month in approximately 2/3 of cases; in other cases it is definitive or slowly improves over several months or even years. Haemodialysis is the

only appropriate treatment. The mechanism of toxicity to one or several toxins remains to be elucidated.

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