Kidney International (2011) **80,** 787–788; doi:10.1038/ki.2011.218

The Case | Multiple-organ failure in a dialysis patient with pericarditis

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Table 1 | Laboratory results 6 days before ICU admission, on ICU admission, and 24 h later

	Normal range	6 days before ICU admission	On ICU admission	24 h after ICU admission
LDH (IU/l)	98–192	216	2521	7260
AST (IU/l)	6–33	33	1570	5330
ALT (IU/l)	14–63	14	464	1361
CK (IU/l)	<200	47	705	798
Troponin I (ng/ml)	<0.08	0.09	1.05	1.24
Lactate (mmol/l)	<2.0	—	14.1	18.0
WBC (10^3/μl)	4.00–10.00	5.57	1.39	1.08
Neutrophils (10^3/μl)	1.60–7.00	3.40	0.83	0.65
Platelets (10^3/μl)	150–350	387	227	160
Reticulocytes (10^3/μl)	30–100	—	9	9
INR	0.8–1.3	1.06	2.08	3.52

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CK, creatine kinase; ICU, intensive care unit; INR, international normalized ratio; LDH, lactate dehydrogenase; WBC, white blood cells.

A 61-year-old man was admitted to the intensive care unit for hypotension and confusion. Hemodialysis was restarted 2 months before because of chronic allograft nephropathy, after 24 years of kidney transplantation for IgA nephropathy. At dialysis initiation, a discrete pericardial effusion was noted. Despite daily dialysis, dry-weight reduction, and reduced anticoagulation, effusion increased and slightly impaired right ventricle function. Pericardocentesis was delayed as colchicine 0.5 mg daily rapidly allowed pain relief and improvement of pericarditis; non-steroidal anti-inflammatory drugs were not associated because of active gastric ulcers. Other long-term medications included cyclosporin (100 mg b.i.d., target trough level ~60 ng/ml), prednisolone (2 mg o.d.), and rosuvastatin (10 mg o.d.). As chest pain recurred 12 days later, colchicine dose was increased to 1 mg o.d. After 7 days without any side effects, the patient suddenly developed diarrhea, confusion, and hypotension. Laboratory results are shown in Table 1. Multiple-organ failure soon developed, with leucopenia, acute liver failure, and rhabdomyolysis. Vasopressors, mechanical ventilation, and continuous veno-venous hemofiltration were initiated. Echocardiography showed a reduced pericardial effusion and no cardiac dysfunction. Bacteriological and imaging studies did not point to any infection. Mesenteric ischemia was suspected, but exploratory laparotomy did not show bowel necrosis. The patient died 36 h after admission from refractory shock. Post-mortem examination was performed.

What is your diagnosis?

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The Diagnosis | **Colchicine poisoning**

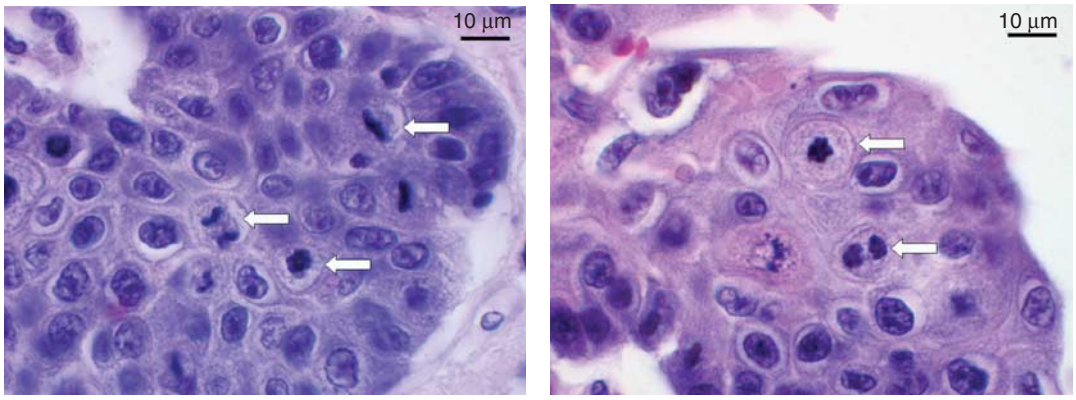

Figure 1 | Post-mortem examination of the esophagus. Light microscopy reveals numerous epithelial cell mitotic arrests at different stages of the cell-division process (arrows), a characteristic feature of colchicine toxicity (hematoxylin–eosin, scale bar = 10 μm).

Postmortem examination revealed numerous mitotic arrests in the esophagus (Figure 1), small bowel, and bone marrow, a characteristic feature of colchicine poisoning.

Colchicine has been used for treating gout and, more recently, familial Mediterranean fever and pericarditis.[1] Colchicine binds to tubulin and disrupts the microtubular network, interfering with the cell-division process. This mechanism accounts for both its anti-inflammatory properties and toxicity. Colchicine poisoning presents in three successive stages: initial gastrointestinal symptoms (day 1), followed by multiple-organ failure, associated with bone-marrow suppression and myopathy (days 2–7), and potentially complete recovery within a few weeks.[2] The diagnosis is difficult, because initial symptoms may suggest enterocolitis or sepsis. Recognition of the toxidrome is the clue to the diagnosis, as there is no established correlation between plasmatic level and severity of illness. In fatal cases, post-mortem examination of tissues with the highest turnover rate—such as gastrointestinal tract and bone marrow—shows numerous epithelial cell mitotic arrests, a characteristic feature of colchicine toxicity.[3]

Physicians should be aware of the potential toxicity of colchicine in chronic kidney disease (CKD) patients. Indeed, gout is frequent in all stages of CKD, including transplant recipients and dialysis patients. Furthermore, these patients are often prescribed more than 10 medications—including statins—to treat comorbid conditions, thus increasing the risk of drug–drug reactions.

Although patients with renal and/or hepatic dysfunction should be considered to be at high risk, colchicine can be well tolerated by some,[1] while others develop severe toxicity. Indeed, the drug disposition has a marked interindividual variability, with a narrow therapeutic-toxicity window. In addition, many drug–drug interactions can increase colchicine exposure.[2] Colchicine elimination is mainly hepatic, and, to a lesser extent, renal. CKD not only impairs renal elimination of many drugs, but also reduces non-renal clearance, leading to an increased bioavailability of drugs predominantly metabolized by the liver.[4] Mechanisms accounting for this fact remain incompletely understood and possibly involve the downregulation of various cytochrome enzymes. Drug disposition results from P-glycoprotein 1, an efflux pump localized in the cell membrane in the intestine, liver, kidney, and blood–brain barrier, and from the intestinal and hepatic CYP3A4 isoform of cytochrome P450. Drug-induced inhibition of these enzymes by macrolides, calcium-channel blockers, calcineurin inhibitors, antifungal agents, or statins can thus decrease colchicine metabolism and increase the risk of colchicine toxicity.

Patients with renal failure and/or medications interfering with colchicine metabolism, such as potent inhibitors of P-glycoprotein 1 and CYP3A4 (cyclosporin in the present case), are at very high risk of poisoning. Colchicine should therefore be avoided, or only used with great caution, in this population. Early recognition of severe colchicine toxidrome should prompt immediate withdrawal of the drug and, if available, considering the use of a specific experimental treatment, Fab fragment antibodies.[2]

DISCLOSURE

All the authors declared no competing interests.

AUTHOR CONTRIBUTIONS

J-FC, DC-Z, LJ, EG, and JM were involved in the clinical care of the patient. SF conducted the histological post-mortem examination. J-FC and JM wrote the manuscript. All authors carefully reviewed the manuscript.

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