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CASE REPORT

BEGINNER

CLINICAL CASE

Colchicine Toxicity

The Fatal Masquerader

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ABSTRACT

Colchicine toxicity results in fatal multiorgan failure. We present a case of colchicine toxicity resulting in transient biventricular failure and cardiogenic shock that were successfully treated with packed red blood cell exchange. (**Level of Difficulty: Beginner.**) (J Am Coll Cardiol Case Rep 2020;2:678–80) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 33-year-old woman presented with 24 h of nausea, vomiting, and abdominal pain. The patient was discharged 36 h earlier after being hospitalized for recurrent pericarditis that was treated with colchicine 0.6 mg twice daily. On admission, she was found to be febrile (temperature 38.6°C) and hypotensive (blood pressure 66/39 mm Hg). Physical examination was otherwise benign. Initial laboratory results revealed leukocytosis (51.2 × 10^9/l), elevated serum lactate (12 mmol/l), acute kidney injury (serum creatinine 2.0 mg/dl), acute transaminitis (alanine aminotransferase 2,148 IU/l, aspartate aminotransferase 4,577 IU/l), and severe coagulopathy (international normalized ratio >15). Serum troponin was within normal limits. Results of a comprehensive toxicology screen were negative. Electrocardiography showed normal sinus rhythm without ST-T changes, and a transthoracic echocardiogram revealed normal biventricular function without valvular disease or pericardial effusion (Video 1). Given her symptoms and preliminary diagnostic findings, sepsis from an intrabdominal source was suspected. The patient was fluid resuscitated, started on broad-spectrum antibiotics, and administered vasopressor therapy. Over the course of 24 h, severe multisystem organ failure developed. She was intubated, paralyzed, and treated with intravascular volume repletion, escalating doses of intravenous vasopressors (epinephrine, norepinephrine, vasopressin), broad-spectrum antibiotics, stress-dose steroids, and high-dose vitamin B_{12} for refractory shock, without improvement.

LEARNING OBJECTIVES

- To recognize that colchicine toxicity results in fatal multisystem organ failure, including severe biventricular failure.
- To acknowledge the need for early, prompt diagnosis and treatment.
- To recognize PRBC exchange as a potential novel therapy.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, or patient consent where appropriate. For more information, visit the *JACC: Case Reports* author instructions page.

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PAST MEDICAL HISTORY

The patient's past medical history included hypertension, pulmonary emboli during long-term anticoagulation, recurrent pericarditis, and polysubstance abuse.

INVESTIGATIONS

A Swan-Ganz catheter was placed, and initial readings were consistent with distributive shock (cardiac output [CO] 7.4 l/min, pulmonary artery diastolic pressure (PAD) 8 mm Hg, systemic vascular resistance indexed [SVRI] 1,572 dynes/s/cm^5/m^2). Within 24 h her hemodynamics rapidly changed, reflecting acute onset cardiogenic shock with high filling pressures (PAD 24 mm Hg), low CO (4.3 l/min), and high systemic vascular resistance (SVRI 2,298 dynes/s/cm^5/m^2). Concomitantly, troponin increased to 73.14 ng/ml, her electrocardiogram was unchanged, and a transesophageal echocardiogram (Video 2) revealed new severe biventricular failure (left ventricular ejection fraction [LVEF] 15%).

DIFFERENTIAL DIAGNOSIS

The differential diagnoses include sepsis with stress induced cardiomyopathy, myocarditis with severe biventricular failure, and colchicine toxicity.

MANAGEMENT

Intravenous milrinone was added for inotropic support and she was started on continuous renal replacement therapy (CRRT) for anuric renal failure. The patient remained hypotensive despite negative blood culture results and improving leukocytosis, which prompted consideration of colchicine toxicity. Packed red blood cell (PRBC) transfusion with 10 U of PRBCS was initiated at 48 h following presentation. At 24 h later, the patient's CO normalized, troponin decreased, and multisystem organ failure improved. Over the next several days, her white blood cell count continued to fall, and she became neutropenic. Repeat echocardiogram completed 6 days after initial decompensation showed recovery of LVEF to 50% to 55%. She was successfully weaned from vasopressors, taken off CRRT, and extubated by day 13. The patient had hair loss on approximately day 24.

Once conscious, the patient admitted to taking 60 tablets of 0.6 mg of colchicine as an intentional overdose. Elevated serum (5.7 ng/ml 30 h after presentation) and whole blood colchicine levels (17 ng/ml, 14 h after presentation) were reported by the laboratory on day 10.

DISCUSSION

Colchicine has been used for more than 2,000 years and is the standard of care for the treatment of acute pericarditis and gout (1). More recently, novel studies, including the COLCOT (Efficacy and Safety of Low-Dose Colchicine After Myocardial Infarction) trial, have shed light on its therapeutic potential in reducing ischemic cardiovascular events in patients with recent myocardial infarction (2). In therapeutic doses, colchicine has pleiotropic properties, with nausea and vomiting as the most commonly noted side effects. However, colchicine also has a narrow therapeutic index with a high mortality rate in supratherapeutic doses. Although mortality often correlates with the ingested dose, a lethal dose is poorly characterized in the published reports.

Patients with colchicine toxicity initially present with gastrointestinal symptoms and rapidly succumb to severe lactic acidosis and multisystem organ failure (1). Once multisystem organ failure ensues, mortality is nearly 100%. The lethality of colchicine is related to its mechanism of action. Colchicine irreversibly binds to unpolymerized tubulin, which is incorporated into microtubules, affecting cellular processes that require cytoskeletal change. This includes neutrophil motility, vesical transportation, and cell mitosis (3).

This report illustrates a case of acute colchicine toxicity caused by an intentional overdose. The patient presented with 24 h of gastrointestinal complaints and rapidly deteriorated, developing refractory shock and multisystem organ failure within hours, followed by cardiovascular collapse from acute myocardial necrosis and biventricular function. This rare case of colchicine toxicity highlights unique cardiovascular findings and emphasizes the importance of prompt diagnosis and immediate treatment.

The pathophysiological mechanisms of colchicine's therapeutic and toxic effects on cardiomyocytes are not well described. It is known that at low levels colchicine inhibit microtubule formation (polymerization), but at high levels the drug promotes microtubule depolymerization. Microtubules are essential to the cardiomyocyte function and are pivotal in mechanosignaling, contractility, and myocyte stiffness. With actin, microtubules constitute the majority of the cardiomyocyte skeleton. They are organized longitudinally around the nucleus, close to the

ABREVIATIONS AND ACRONYMS

CO = cardiac output

CRRT = continuous renal replacement therapy

LVEF = left ventricular ejection fraction

PAD = pulmonary artery diastolic pressure

PRBC = packed red blood cell

RBC = red blood cell

SVRI = systemic vascular resistance indexed

mitochondria and plasma membrane, in a dynamic transportation system, which makes them central to cardiomyocyte signaling. At the cytoskeletal level, microtubules are constantly turned over through polymerization and depolymerization to assist with contraction. In cardiomyocytes, only 30% of microtubules are polymerized at 1 time (4). It can be hypothesized that complete depolymerization of microtubules by colchicine impedes cardiomyocyte functioning at multiple levels. Studies report that treatment of diseased myocardium with therapeutic doses of colchicine decreases stiffness, improves contractility, and boosts CO (5). Other studies report the effect of colchicine on excitation-contraction coupling and calcium fluxes (5).

Colchicine toxicity is difficult to treat, with no universally agreed-on antidote. Anticholchicine antibodies have been used in at least 1 patient previously; however, they are available only on an experimental basis (6). Enhanced elimination options are limited because of the agent's large volume of distribution, concentration within erythrocytes, and protein affinity. In earlier reports, plasmapharesis was also ineffective. In 1 case, whole blood exchange transfusion was performed within 10 h, and the patient survived despite consuming >0.8 mg/kg, a dose historically reported to have a 100% mortality (6). To date, the consensus is that once multiorgan failure ensues, no treatment modality has proven to be effective. In our patient, we performed PRBC transfusion approximately 48 h after her colchicine ingestion. No one has evaluated the ability of red blood cell (RBC) exchange to remove colchicine in an anuric patient. Serum and whole blood levels before RBC exchange were 5.7 and 17 ng/ml, respectively. Post-exchange, a repeat whole blood level returned at 7.6 ng/ml. Of note, this patient consumed 36 mg or 0.27 mg/kg of colchicine. This may represent slower than expected elimination, but studies suggest that as much as 30% of colchicine is renally cleared (7). Our data suggest that RBC exchange reduced whole blood levels in our anuric patient, whereas plasma levels remained unchanged (5.7 ng/ml 30 h after presentation to 5.3 ng/ml 29 h later). This finding confirms concentrated colchicine levels within the RBCs and unchanged plasma levels from colchicine redistribution. Despite the presence of multiorgan failure with sustained treatment on CRRT and 3 vasopressors, the patient had complete recovery by targeting the RBCs as a reservoir for the colchicine body burden.

FOLLOW-UP

The patient spent a total of 15 days in the intensive care unit. She was weaned from pressors and CRRT on hospital day 10 and was successfully extubated on hospital day 13. She was discharged after a nearly 3-week hospital stay with complete renal, hepatic, and cardiac recovery. She entered outpatient rehabilitation and has not had any further sequelae from her hospital course.

CONCLUSIONS

This case highlights the cardiovascular implications of colchicine toxicity, hypothesizes the pathologic mechanism of toxicity, stresses the importance of early diagnosis, and describes PRBC exchange as a novel treatment for colchicine toxicity.

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KEY WORDS biventricular failure, cardiogenic shock, colchicine toxicity, packed red blood cell exchange

APPENDIX For supplemental videos, please see the online version of this paper.