Case study

A Possible Colchicine Poisoning

Abstract

We have experienced a case of colchicine toxicity presenting with rapidly progressive gastrointestinal symptoms, hemodynamic instability, and multiple organ failure.

An 86-year-old Japanese man presented to our hospital with subarachnoidal hemorrhage transferring from another hospital where he had been treated with colchicine 0.5 mg three times daily for an elevated uric acid level. During his admission, he had a nosocomial COVID-19 infection. Then, he developed loss of appetite, and significant diarrhea, which continued for two days. He then developed shock and hypoxia and was transferred to intensive care unit (ICU). The laboratory data revealed pancytopenia, acute kidney injury, lactic acidosis, marked coagulopathy, elevated troponin I , and C-reactive protein with poor cardiac function and hypotension refractory to vasopressors. Despite intensive care, he expired on 2nd day of ICU admission. Because his cardiac function was depressed from the beginning and was not respond to inotropic support, direct myocardial damage, rather than septic cardiomyopathy was suspected. We, therefore, emphasize that colchicine poisoning should be suspected in patients with access to the drug and the typical toxidrome.

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Introduction:

The anti-inflammatory agent colchicine is used mainly for the treatment and prevention of gout and familial Mediterranean Fever (FMF). It has a narrow therapeutic index and unintentional colchicine toxicity is uncommon, but often associated with a poor outcome. We have experienced a case with rapidly progressed gastrointestinal symptoms, hemodynamic instability, and multiple organ failure due to possible colchicine toxicity.

Case Presentation

An 86-year-old gentleman presented for treatment of subarachnoidal hemorrhage (SAH) with referring from another hospital. In his past medical history, the patient was suffered from sick sinus syndrome, which was treated with pacemaker implantation, congestive heart failure. During hospitalized at our hospital, the patient had a high uric acid level with mild gout attack that wastreated with colchicine 0.5 mg three times dailyfor 2 weeks without any uric acid lowering medicine. After successful treatment for his SAH, the patient was diagnosed with COVID-19 infectiondue to close contact without any symptoms. Because of his high risk for COVID-19 infection, he was treated with Remdesivir and corticosteroid, and then he started to have significant diarrhea with a loss of appetite with mildly impaired renal function (Creatinine 1.21 mg/dl), mildly increased C-reactive protein (CRP 2.77 mg/dl) and thrombocytopenia (73,000 /µL). These symptoms were continued for the next 2 days, although drip infusion was applied. Then the patient suddenly had shock status (ABP 75/40 mmHg) with desaturation (SAT 87 %) and was transferred into the ICU. The laboratory data showedsignificant coagulopathy(international normalized ratio >1.51), acute kidney

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injury(eGFR 19.6, serum creatinine 2.68 mg/dL), lactic acidosis (24.3 mmol/L) as well as pancytopenia. Troponin I was highly elevated (148 pg/mL) and CRP was elevated (20.78 mg/dL). Electrocardiography showed normal sinus rhythm with some pacing waves and premature ventricular contractions without ST-T changes. Given his symptoms and preliminary diagnostic findings, septic shock was suspected. The patient was fluid resuscitated, started on broad-spectrum antibiotics, and administered norepinephrine and vasopressin therapy. Over 24 hours, the patient remained in severe hypotension with peripheral circulatory failure with very high lactate (25.4 mmol/L) and severe multisystem organ failure developed. He was intubated, paralyzed, and treated with intravascular volume repletion, escalating doses of intravenous vasopressors (dobutamine, norepinephrine, vasopressin), broad-spectrum antibiotics, stress-dose steroids for refractory shock without improvement. The patient presented refractory hypoglycemia and low bicarbonate, which were treated with multiple-dose of bolus glucose and bicarbonate.

On the 2nd day of ICU accommodation, blood tests showed significantly elevated transaminase (AST 1576 U/L, ALT 504 U/L), ALP (504 U/L), BUN (78.2 mg/dL), creatinine (3.17 mg/dL) suggesting further deterioration of acute kidney injury and a liver damage.Flotrac sensor was applied to monitor cardiac output, and the initial reading was low cardiac index (1.5 L/min/m^2). Within the next few hours, his hemodynamics were severely debilitated with wider QRS, reflecting progressive myocardial injury. A transthoracic echocardiogram revealed severe biventricular failure (left ventricular ejection fraction [LVEF]<10 %). On admission, an echocardiogram revealed relatively good biventricular function (EF 65 %) with mild anteroseptal hypokinesis, moderate mitral regurgitation with

backward pulmonary hypertension (ePAP>70 mmHg), severe tricuspid regurgitation. At that time, colchicine toxicity was highly suspected. He was started on continuous renal replacement therapy (CRRT) for anuric renal failure. Packed red blood cell (PRBC) transfusion with platelet-rich plasma (PRP) was administered. Despite our management, his condition was debilitated without recovery. He was expired on the second day of ICU admission.

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DISCUSSION

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This patient presented us with severe progressive hypotension, pancytopenia, GI symptomsand high CRP. It was suspected septic shock initially, however high troponine I, leukocytopenia and anemia does not occur in initial phase of septic shock and most septic cardiomyopathy would be reversible. Gastrointestinal symptoms are also not popular in septic shock. These negative evidence may suggest possible colchicine toxicity, since colchicine poisoning is mostly diagnosed based on comprehensive clinical findings..

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Colchicine has been used for the treatment of acute pericarditis, gout, and familialMediterranean fever[3].In therapeutic doses, colchicine has pleiotropic properties, with nausea and vomiting as the most commonly noted side effects.Colchicine does not have a uric acid lowering action, but has an anti-inflammatory effect. Colchicine also has a narrow therapeutic index with a high mortality rate in supratherapeutic doses. The usual adult oral doses for acute gout is 1.2 mg/day and for gout prophylaxis is 0.5-0.6 mg/day three to four times a week. High fatality rate was reported after acute ingestions exceeding 0.5 mg/kg. The lowest reported lethal doses of oral colchicine are 7-26 mg[4].

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[5].Gastrointestinal symptoms might cause dehydration and/or pre-renal azotemia, which caused increased level of colchicine.The pathophysiological mechanisms of colchicine's therapeutic and toxic effects on cardiomyocytes are not well described. It is known that at low levels colchicine inhibits microtubule formation (polymerization), but at high levels, the drug promotes microtubule depolymerization. Microtubules are essential to cardiomyocyte function and are pivotal in mechanosignaling, contractility, and myocyte stiffness. Other studies report the effect of colchicine on excitation-contraction coupling and calcium fluxes[6]. Colchicine toxicity is difficult to treat, with no universally agreed-on antidote. It has been reported that troponin I is a reliable parameter for prediction of cardiovascular collapse in acute colchicine overdose[7].Previous study[8] among 3302 patients, 43 (1.30 %) were inappropriately prescribed colchicine. Of these 43 patients, 11 had baseline renal and/or liver impairment. Our patient had mildly impaired renal function (Cr. 1.05-1.33 mg/dL) on admission.

Based on our findings we emphasize that colchicine poisoning should be suspected inpatients with access to the drug and the typical toxidrome (gastroenteritis, hypotension, lactic acidosis, and prerenal azotemia), particularly in patient with renal impairment.It is imperative to recognize its features as it is associated with a high mortality rate when missed.

Informed consents were obtained and this study was approved by our ethical committee and comply with the ethical principles of the Helsinki declaration.

References:

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Table 1. Blood Test Data on ICU admission

	Results	Normal range	units
Total bilirubin	1.3	0.3-1.2	g/dL
Blood Urea Nitrogen	75.6	8-23	mg/dL
Creatinine	2.68	0.61-1.08	mg/dL
Uric Acid	8.5	3.8-7	mg/dL

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Calcium	7.2	8.5-10.2	mg/dL
Inorganic Phosphate	4.9	2.5-4.5	mg/dL
C-Reactive Protein	20.78	0-0.3	mg/dL
White Blood Cell	15	40-85	$X10^2/\mu L$
Red Blood Cell	285	415-550	$x10^4/\mu L$
Hemoglobin	9.3	13.5-17.5	g/dL
Hematocrit	27.5	39-51	%
Platelet	0.3	12-36	$X10^4/\mu L$
D-dimer	20.4	0-1.0	µg/mL
Troponin I	148	0-26	pg/mL
Brain Natriuretic Peptide	1336.5	0-18.4	pg/mL
Estimated Glomerular Filtration Ratio	18.4	>60	$mL/min/m^2$