## THE PATIENT
58-year-old female

## SIGNS & SYMPTOMS
– Gout exacerbation
– Progressive weakness
– Hypotension

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## THE CASE
A 58-year-old female came to the emergency department (ED) because she had progressive weakness, hypotension, and altered mental status. In the ED she had a heart rate of 107 beats per minute; blood pressure, 96/68 mm Hg; respiratory rate, 20 breaths per minute; oxygen saturation, 96%; and a 96.7°F temperature that spiked to 101.6°F. The absolute neutrophil count (ANC) was 1500 cells/mm$^3$, hemoglobin was 13 g/dL, and platelet count was 95 × 10$^9$/L. Her serum creatinine was 2.5 mg/dL (baseline of 1.0) and cyclosporine concentration was <25 ng/mL.

Our patient had a history of renal transplant, gout, and chronic kidney disease. Her medications included bumetanide, clonazepam, colchicine .6 mg BID, a therapeutic dose of cyclosporine, flurazepam, gabapentin, levothyroxine, mirtazapine, oxycodone, prednisone, and premarin. Three days before she came to the ED, she experienced a gout exacerbation and took six .6 mg doses (3.6 mg total) of colchicine that resulted in severe diarrhea. The next day, she took 3 mg of colchicine and had more severe diarrhea and a fever. Our patient took another 1.2 mg of colchicine the next day and developed the progressive weakness, hypotension, and altered mental status that led her to seek care in the ED.

## THE DIAGNOSIS
Our patient was admitted to the hospital with a diagnosis of pancytopenia and presumed sepsis and intravenous broad-spectrum antibiotics were administered. Blood, urine, and sputum cultures, stool studies, and chest x-ray were negative for pneumonia. A peripheral blood smear revealed dysplastic-appearing neutrophils with vacuolization, which is characteristic of colchicine toxicity, myelodysplastic syndromes, or acute leukemia. However, the absence of blast cells in the peripheral blood smear and the normal appearance of the liver and spleen on a subsequent abdominal ultrasound refuted a primary hematologic disorder. Thus, based on the patient's recent colchicine use and subsequent progressive pancytopenia and sepsis, we diagnosed colchicine toxicity in this patient.

## DISCUSSION
Colchicine is a potent anti-inflammatory drug that has a narrow therapeutic index. Indicated for treating gout and familial Mediterranean fever, it inhibits mitosis by interfering with microtubule formation and arresting cell division. Colchicine is rapidly absorbed in the gastrointestinal (GI) tract and undergoes first-pass hepatic metabolism with enterohepatic recirculation of metabolites prior to excretion via the biliary tract.[1] Ten percent to 20% of colchicine is excreted by the kidneys.[2]

**Colchicine toxicity begins with GI symptoms,** such as diarrhea, is followed by falling peripheral blood cell counts and altered mental status. A late sign of colchicine toxicity is alopecia. If the toxicity is left unchecked, multi-organ dysfunction that mimics severe sepsis will occur, resulting in death.[3]

CONTINUED

Toxicity typically occurs at doses of .5 mg/kg/d. Fatal overdose from colchicine has been described in patients taking as little as 7 mg; however, survival from a 60-mg overdose has been reported.[1] In a review of 150 patients who overdosed on colchicine, a single dose of .8 mg/kg was universally fatal.[4] Therapeutic doses of colchicine have resulted in severe toxicity in patients with hepatic or renal dysfunction.[5,6]

## Toxicity risk is increased in patients taking immunosuppressants

Colchicine toxicity from therapeutic doses may occur in patients taking concomitant immunosuppressive drugs, particularly cyclosporine. In case series, patients taking stable doses of cyclosporine and prophylactic doses of colchicine exhibited toxicity when they took therapeutic doses of colchicine for gout exacerbations.[7,8] Another case series described 2 post-renal transplant patients, immunosuppressed with azathioprine and prednisone, who had comorbid familial Mediterranean fever and were maintained on colchicine prophylaxis.[9] When they converted to cyclosporine for immunosuppression, each patient began to demonstrate GI and muscular symptoms of colchicine toxicity. Upon discontinuing cyclosporine, the GI and muscular symptoms rapidly resolved.[9]

**How cyclosporine interacts with colchicine.** Cyclosporine is a potent CYP3A4 and P-glycoprotein inhibitor, and colchicine is a CYP3A4 and P-glycoprotein substrate. In vivo studies have demonstrated that cyclosporine inhibits hepatic and renal clearance of colchicine, thus increasing serum colchicine levels, further lowering the toxic colchicine dose.[10,11]

**Our patient.** The prophylactic dosage of colchicine our patient had been taking before her recent gout flare (.6 mg BID) was higher than the adjusted dose recommended to treat gout flares for patients taking cyclosporine (a single .6 mg dose to be repeated no earlier than 3 days).[4] The dosages she took to treat her flare far exceeded this recommendation.

As a result, our patient developed severe colchicine toxicity. During her hospitalization, our patient's cell counts continued to fall, requiring blood and platelet transfusions; her ANC nadir was 14 cells/mm$^3$. She continued to have progressive multi-organ failure and developed alopecia. Management revolved around supportive measures for all of the end-organ effects.

Our patient died on hospital Day 7. Contributing factors included premorbid immunosuppression, renal insufficiency, and concomitant P-glycoprotein and CYP3A4 inhibition.

**Colchicine toxicity from therapeutic doses may occur in patients taking concomitant immunosuppressive drugs—particularly cyclosporine.**

## THE TAKEAWAY

Colchicine toxicity from therapeutic doses may occur in patients taking concomitant immunosuppressive drugs. Physicians who prescribe colchicine should be aware of these additional risks and adjust dosages accordingly. Activated charcoal can be given for acute overdose. JFP


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