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REVIEW

Colchicine poisoning: the dark side of an ancient drug

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Introduction. Colchicine is used mainly for the treatment and prevention of gout and for familial Mediterranean fever (FMF). It has a narrow therapeutic index, with no clear-cut distinction between nontoxic, toxic, and lethal doses, causing substantial confusion among clinicians. Although colchicine poisoning is sometimes intentional, unintentional toxicity is common and often associated with a poor outcome. *Methods*. We performed a systematic review by searching OVID MEDLINE between 1966 and January 2010. The search strategy included "colchicine" and "poisoning" or "overdose" or "toxicity" or "intoxication." *Toxicokinetics.* Colchicine is readily absorbed after oral administration, but undergoes extensive first-pass metabolism. It is widely distributed and binds to intracellular elements. Colchicine is primarily metabolized by the liver, undergoes significant enterohepatic re-circulation, and is also excreted by the kidneys. *Therapeutic and toxic doses.* The usual adult oral doses for FMF is 1.2–2.4 mg/day; in acute gout 1.2 mg/day and for gout prophylaxis 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. *Drug interactions.* CYP 3A4 and P-glycoprotein inhibitors, such as clarithromycin, erythromycin, ketoconazole, ciclosporin, and natural grapefruit juice can increase colchicine concentrations. Co-administration with statins may increase the risk of myopathy. *Mechanisms of toxicity.* Colchicine's toxicity is an extension of its mechanism of action – binding to tubulin and disrupting the microtubular network. As a result, affected cells experience impaired protein assembly, decreased endocytosis and exocytosis, altered cell morphology, decreased cellular motility, arrest of mitosis, and interrupted cardiac myocyte conduction and contractility. The culmination of these mechanisms leads to multi-organ dysfunction and failure. *Reproductive toxicology and lactation*. Colchicine was not shown to adversely affect reproductive potential in males or females. It crosses the placenta but there is no evidence of fetal toxicity. Colchicine is excreted into breast milk and considered compatible with lactation. *Clinical features*. Colchicine poisoning presents in three sequential and usually overlapping phases: 1) 10–24 h after ingestion – gastrointestinal phase mimicking gastroenteritis may be absent after intravenous administration; 2) 24 h to 7 days after ingestion – multi-organ dysfunction. Death results from rapidly progressive multi-organ failure and sepsis. Delayed presentation, pre-existing renal or liver impairment are associated with poor prognosis. 3) Recovery typically occurs within a few weeks of ingestion, and is generally a complete recovery barring complications of the acute illness. *Diagnosis.* History of ingestion of tablets, parenteral administration, or consumption of colchicine-containing plants suggest the diagnosis. Colchicine poisoning should be suspected in patients with access to the drug and the typical toxidrome (gastroenteritis, hypotension, lactic acidosis, and prerenal azotemia). *Management.* Timely gastrointestinal decontamination should be considered with activated charcoal, and very large, recent (<60 min) ingestions may warrant gastric lavage. Supportive treatments including administration of granulocyte colony-stimulating factor are the mainstay of treatment. Although a specific experimental treatment (Fab fragment antibodies) for colchicine poisoning has been used, it is not commercially available. *Conclusion.* Although colchicine poisoning is relatively uncommon, it is imperative to recognize its features as it is associated with a high mortality rate when missed.

Keywords Colchicine; Poisoning; Toxicity; Overdose; Colchicum autumnale

Introduction

Colchicine is a neutral lipophilic alkaloid with weak anti-inflammatory activity. It is extracted from two plants: *Colchicum autumnale* (autumn crocus, meadow saffron) and *Gloriosa superba* (glory lily). Colchicine has been used for centuries for the treatment of acute gout and has been approved by the FDA for gout prophylaxis and treatment of familial Mediterranean fever (FMF), in which it can reduce the incidence of

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the primary complication, systemic amyloidosis.[1] Colchicine may also play a role in the treatment of various other conditions such as recurrent pericarditis, scleroderma, Behcet's syndrome, and Sweet's syndrome but the data are often limited and inconclusive.[2,3]

The use of colchicine is limited by its toxicity. It is safe when administered according to established therapeutic guidelines in FMF. However, gastrointestinal side effects can occur before the relief of acute gouty pain even when using recommended doses.[4,5] At excessive doses, colchicine can cause serious systemic toxicity. Acute colchicine poisoning is uncommon, but is associated with a high mortality rate. It is essential, therefore, that clinicians recognize and are familiar with colchicine poisoning.

The objective of this article is to review colchicine poisoning, as early diagnosis and treatment can favorably influence the prognosis of this potentially fatal intoxication.

Methods

We performed a systematic review by searching OVID MEDLINE between 1966 and January 2010. Our search strategy included "colchicine" and "poisoning" or "overdose" or "toxicity" or "intoxication." This search identified 194 papers. This list was manually screened for papers relating to colchicine poisoning in humans, the mechanism of toxicity, or its clinical management. Seventy-six papers were identified as meeting the search criteria. Reference lists of identified papers were also manually screened for additional references (identifying an additional 32). Nonpeer-reviewed sources were also searched and four were included.

Toxicokinetics

Colchicine is rapidly absorbed from the gastrointestinal tract. Serum concentrations peak at 0.5–3.0 h after ingestion.[6] Absorption is not significantly delayed even following an overdose.[7] The drug undergoes extensive hepatic first-pass metabolism, which accounts for its relatively low systemic bioavailability, 25–50%.[8–10] After absorption, colchicine is rapidly distributed to all tissues, where it binds to intracellular elements. In therapeutic doses, its protein binding is 10–50% and volume of distribution ranges between 2 and 12 L/kg[11,12] but reaches up to 21 L/kg in overdose.[7] Colchicine is eliminated primarily by hepatic metabolism by the CYP 3A4 isoform of cytochrome P450, which involves deacetylation and demethylation, followed by biliary excretion.[13,14] Colchicine and its metabolites undergo significant enterohepatic re-circulation.[11,15–17] The kidneys have an important role in the clearance of colchicine, and the drug's clearance is significantly reduced in patients with renal and hepatic insufficiency.

Patients with impaired renal or hepatic function are at higher risk for toxicity and need to be closely monitored even while receiving conventional dose regimens.[11,12,18,19] Additionally, drugs such as clarithromycin and ciclosporin which inhibit P-glycoprotein (P-gp), an integral membrane ATPase efflux pump encoded on the *MDR1* (*ABCB1*) gene, can also potentiate colchicine toxicity. Inhibition of P-gp induces both increased gastrointestinal absorption and decreased efflux (e.g., from hepatocytes) leading to increased serum and intracellular colchicine concentrations. The high intracellular concentration results in greater tubulin inhibition and enhanced toxicity.[20,21]

The mean elimination half-life of oral colchicine is 4.4–16 h in therapeutic doses and may reach 11–32 h in poisoned patients.[7,12] Colchicine can be detected in leukocytes and in the urine for at least 9 days following a single intravenous (IV) dose.[22] Its half-life in leukocytes is reported to be 60 h.[23] According to postmortem tissue analyses, colchicine accumulates at high concentrations in bone marrow, testicles, spleen, kidney, heart, liver and gastrointestinal tract, lung, and brain.[7]

Therapeutic and toxic doses

There are several dosing regimens for FMF and acute gout and treatment prophylaxis. Typical oral recommended doses of colchicine for FMF range between 1.2 and 2.4 mg/day, whereas the recommended dose for acute gout is 1.2 mg followed by a single dose of 0.6 mg at the first sign of flare, and for gout prophylaxis 0.5–0.6 mg/day three to four times a week.[23] In children with FMF, the dosage should be adjusted to body weight and ranges from 0.3 to 1.8 mg/day in children between 4 and 6 years and 0.9 to 1.8 mg/day in children between 6 and 12 years (older children are administered adult doses) and may be increased up to 2 mg/day if attacks are not controlled.[24] Tablets contain colchicine 0.6 or 1.0 mg,[23] and an IV solution (0.5 mg/mL) is also available in some countries.

IV colchicine is occasionally administered when a rapid response is desired or the oral route is precluded; however, the FDA recently withdrew marketing approval for IV preparations.[25] The risk of severe systemic poisoning with IV administration of the drug is significantly increased, partly because of lack of early gastrointestinal symptoms.[26–28] If IV colchicine is given as a substitute for the oral form, it should not exceed 50% of the oral dose because of lack of first-pass effect.[26] Toxicity in these cases depends on the total cumulative dose given in a course, which should not exceed 2–4 mg in adults; no colchicine (by any route) should be given for 7 days thereafter.[27] The failure to follow these guidelines (with doses of 5.5–19 mg being administered) led to severe poisoning and death at 1–40 days after IV drug administration in 20 adults between 1983 and 2000.[27] The dose should be avoided or significantly reduced in patients with kidney failure.

In general, the risk of colchicine poisoning is dose-dependent. However, the drug has a low therapeutic index, and there is overlap between therapeutic and toxic doses and a high fatality rate when ingestion exceeds 0.5 mg/kg in acute cases.[29,30] Gastrointestinal and coagulation disorders were reported in

doses less than 0.5 mg/kg, bone marrow aplasia and a 10% mortality rate in patients ingesting 0.5–0.8 mg/kg, and death in doses exceeding 0.8 mg/kg in acute ingestions.[29] Colchicine exhibits a great variation in the dose required to cause significant morbidity or mortality. There is no clear-cut line between nontoxic, toxic, and lethal doses of colchicine in either adults or children.

The lowest reported lethal doses of oral colchicine have ranged from 7 to 26 mg.[31–35] Fatalities have also been reported following IV injection of 18 mg over 11 days, 10 mg over 5 days, and 8 mg over 3 days.[28,36,37] In contrast, adult patients survived acute ingestions of up to 60 mg.[38] The youngest patient with a fatal colchicine overdose was reported as 12 months old.[39] However, each of these is a case report, and the generalizability of observations is limited.

Of interest is a 1966 report describing the survival of a patient after an alleged "ingestion of 350 mg of colchicine,"[40] which has been repeatedly quoted in the medical literature over the past 40 years.[41–43] This report was of a young woman who ingested boiled tubers of *G. superba*, developed colchicine poisoning, and fully recovered. We believe the authors overestimated the amount of colchicine in the tubers. Survival after ingestion of colchicine 350 mg is inconceivable in view of the minimal lethal oral doses reported (7–26 mg)[31–35] and the maximal reported tolerated dose of 60 mg.[38] Misquotation of this overestimation can result in reduced alertness to much lower but still life-threatening colchicine overdose.

Drug interactions

Interactions between colchicine and drugs or compounds that inhibit CYP 3A4 can potentially lead to increased serum and tissue colchicine concentrations and toxicity. The main specific inhibitors of CYP 3A4 known to interact with colchicine are clarithromycin, erythromycin, ketoconazole, and natural grapefruit juice, although multiple other inhibitors may interact with the drug.[41,44–47] P-gp inhibitors reported to interact with colchicine include clarithromycin[44,46,48] and ciclosporin.[49–51] Concurrent use of P-gp or strong CYP 3A4 inhibitors with colchicine is contraindicated in patients with hepatic or renal impairment[23] and a dose reduction or interruption of colchicine therapy should be considered in patients taking those inhibitors who have no renal or hepatic impairment. Concomitant administration of colchicine and statins (i.e., fluvastatin, lovastatin, and pravastatin) resulted in myopathy.[52–54] The mechanism for this interaction has not been fully elucidated but may involve disruption of the cytoskeleton by both the statin and colchicine.[52]

Mechanisms of toxicity

Colchicine binds to the intracellular protein tubulin, preventing its alpha and beta forms from polymerizing to form microtubules. This disruption of the microtubular network results in impaired protein assembly in the Golgi apparatus, decreased endocytosis and exocytosis, altered cell shape, depressed cellular motility, and arrest of mitosis. In toxic doses, colchicine arrests mitosis in metaphase because chromosome separation depends on microtubular function,[16,55] thus inhibiting cell division. These effects occur in all cell lines of the body and explain both the therapeutic effects and the multi-organ toxicity seen with poisonings. The systems with the highest turnover rate, that is, bone marrow, gastrointestinal tract, and hair follicles, are the most vulnerable and most readily affected.[56,57]

Disruption of the microtubular network also leads to decreased expression of adhesion molecules on neutrophil membranes and modulates cytokine production.[58] Colchicine may also have a direct toxic action on myocardial cells. This effect may be related to binding of the drug to microtubules in myocytes, which interferes with cardiac conduction and contractility.[59–63] The inhibition of other important microtubular functions such as cytoplasmic motility and extracellular secretion of hormones and neurotransmitters may be involved in the devastating processes leading to multi-organ failure in cases of drug overdose.[64] Colchicine also inhibits the release of histamine from mast cells, inhibits the secretion of insulin from the pancreas, depresses central respiratory centers, induces hypertension by central vasomotor stimulation, and enhances the patient's response to sympathomimetic agents.[65]

Recent studies have focused on the role of P-gp in colchicine poisoning because this transporter is an efflux protein.[66] The paucity of P-gp expression in neutrophils, together with the threefold greater concentration of colchicine detected in neutrophils compared to lymphocytes, may explain the mechanism of action of colchicine.[58] This also suggests that P-gp is an important factor in colchicine toxicity and can partly explain neutropenia and bone marrow suppression.

Reproductive toxicology and lactation

Sperm motility, which depends on microtubular function, may theoretically be reduced by colchicine. However, *in vitro* studies showed that the serum concentration required to impair sperm motility is 3,000 times higher than the concentration achieved with therapeutic dosing.[67] The reported frequency of oligospermia in adult patients treated with colchicine ranges widely, from 0% to 37%, depending on the series and the underlying disease.[16,24,68,69] Recent data suggest that this effect is rare.[70] There is no convincing evidence of a negative effect of colchicine treatment on female fertility. In fact, by controlling attacks in pregnant women with FMF, colchicine may reduce peritoneal adhesions and mechanical infertility.[70]

Small amounts of colchicine were found in cord blood samples, suggesting that it may cross the human placenta.[71] Several case series have not demonstrated any effect on birth weight, duration of pregnancy, miscarriage rate, or congenital malformations.[70,72–75] Furthermore, in 548 pregnant women treated chronically with colchicine for FMF, the rate of birth defects

and chromosomal abnormalities were consistent with the general population.[76] This large study suggests that the small number of case reports linking colchicine to Down syndrome may simply reflect chance alone.[65,74,77] Most current policies recommend continuous colchicine therapy during pregnancy with amniocentesis performed in the fourth to fifth month.[76,78]

Colchicine is present in breast milk and can bind to fatty acids and proteins.[79–81] Concentrations in milk have a parallel time–concentration curve to that of plasma.[81] The estimated daily amount of colchicine ingested by the nursing infant is less than one-tenth the therapeutic dose (per kilogram).[16] This finding, together with the favorable outcome of more than 50 infants breast fed by colchicine-treated mothers, have led to many authors recommending continued breast-feeding in this scenario.[16] The American Academy of Pediatrics categorizes colchicine as compatible with breast-feeding.[82]

The potential effect of colchicine on childhood growth is also of concern, as growth requires cell division. However, one study found that growth was within the normal percentiles even in children treated with colchicine (0.5–1 mg/day) for long periods.[24] Further evaluation of this cohort demonstrated that their development and fertility were also normal.

Clinical features

Patients ingesting therapeutic oral doses of colchicine may suffer from abdominal pain, cramping, hyperperistalsis, diarrhea, nausea, and vomiting.[23,44] Gastrointestinal manifestations develop frequently and may precede pain relief in up to 91% of patients, limiting enthusiasm for the drug generally, and limiting its dose in many patients.[5] The suggestion to administer colchicine at frequent intervals until gastrointestinal side effects develop is a matter of significant concern[4] and has led to unintentional death in our experience.

The clinical course of acute colchicine poisoning is well described (Table 1). It may be divided into three sequential and usually overlapping phases.[16,64] The *first (gastrointestinal) phase* reflects gastrointestinal mucosal damage and a cholera-like syndrome may develop.[33,35,64,83–88] Gastrointestinal symptoms may be limited when toxicity follows IV administration.[26–28] The *second (multi-organ) phase* is characterized by multi-organ dysfunction and metabolic derangements are also common.[17,35,44,56,64,84,89,90] Death from acute colchicine poisoning is usually due to hemodynamic collapse and cardiac arrhythmias (typically 24–36 h after ingestion or could be sudden) or from infectious or hemorrhagic complications.[17,91–96] Patients with early hemodynamic collapse have a particularly poor prognosis.[91] Surviving patients will enter the *third phase,* which is characterized by recovery of bone marrow depression with rebound leukocytosis, resolution of organ failure, and can be followed by complete recovery.[30,37,44,97] Myopathy, neuropathy, and combined myoneuropathy have all been reported after acute poisoning. Proximal limb weakness, distal sensory abnormalities, distal areflexia, and nerve conduction impairment compatible with

Table 1. Clinical stages of colchicine poisoning

Stage	Time of onset	Features
1. Gastrointestinal phase	0–24 h post-ingestion	Nausea, vomiting, diarrhea, abdominal discomfort
		Hypovolemia
		Leukocytosis
2. Multi-organ failure phase	1–7 days post-ingestion	Respiratory distress syndrome
		Cardiac arrhythmias, failure, arrest
		Encephalopathy, brain edema
		Convulsions
		Renal failure
		Liver failure
		Disseminated intravascular coagulation
		Bone marrow suppression
		Pancytopenia
		Hemolysis
		Metabolic derangements: metabolic acidosis, hypokalemia, hyponatremia, hypoalcemia, hypoglycemia (or hyperglycemia), hypophosphatemia
		Myopathy
		Neuropathy
		Secondary sepsis
3. Recovery phase	7–21 days post-ingestion	Resolution of organ system derangements
		Rebound leukocytosis
		Alopecia

Modified from Finkelstein.[113]

axonal neuropathy are characteristics.[42,64,90,98,99] Other complications include delirium, stupor and coma, convulsions, adrenal hemorrhage, disseminated intravascular coagulopathy, alopecia, and pancreatitis.[29,30,41,42,90,99–101] Although rare, a toxic epidermal necrolysis-like reaction has also been reported, with histopathology showing subepidermal bullae and apoptosis of keratinocytes.[34]

Similar to the third phase of acute poisoning described above, chronic colchicine toxicity includes neuromyopathy and myocardial failure. The neuromyopathy presents with proximal weakness and can also include respiratory insufficiency.[102] An increase in serum creatine kinase activity is invariably observed. These features should reverse in 3–4 weeks after discontinuation of colchicine.[102] The presence of myocardial failure offers a dismal prognosis.[93] Chronic toxicity is thought to be rare because development of gastrointestinal symptoms usually leads to stopping treatment.[93] Chronic toxicity is often associated with renal impairment or precipitated by an inter-current illness and is usually misdiagnosed as polymyositis or uremic neuropathy.[35,98,102] The best predictor for myotoxicity from colchicine was found to be impaired renal function, with a creatinine clearance of 50 mL/min or less.[103]

Diagnosis

Colchicine poisoning constitutes a toxicological emergency and requires rapid intervention. The diagnosis of colchicine poisoning is not difficult if a history of ingestion or parenteral administration is available. Colchicine can also be unintentionally consumed in meals in the form of the leaves of *C. autumnale* and the tubers of *G. superba* as they can be mistaken for wild garlic and sweet potatoes, respectively.[30,84,85,104,105] In regions where FMF is endemic and colchicine use is common, physicians should maintain a high index of suspicion, because symptoms of colchicine may be misdiagnosed for other systemic diseases (e.g., enterocolitis). A diagnosis of colchicine poisoning should be investigated when a patient presents with the typical colchicine toxidrome (gastroenteritis, hypotension, lactic acidosis, and prerenal azotemia).[47] Differentiation of colchicine poisoning from enterocolitis, sepsis, nonsteroidal anti-inflammatory drug or iron poisoning (in the early phase), or heavy metal poisoning (in the later phase) is possible by the presence of severe bone marrow suppression in the second phase and proper infectious and relevant toxicological evaluations. Under-diagnosis may partly explain the small number of reported cases of colchicine poisoning.

Any patient with a known or suspected colchicine overdose should be admitted for observation for 24 h and managed as an inpatient.[30] Early gastrointestinal manifestations should be sought. If no symptoms and signs develop within the first 24 h after ingestion they are unlikely to appear later, and the patient may be discharged. In cases of IV colchicine overdose, gastrointestinal signs are lacking, and a higher index of suspicion and longer observation period (a few days) are needed. If clinical signs of poisoning develop, close monitoring in an intensive care unit is required, anticipating the above-mentioned complications.

Laboratory studies

Baseline laboratory studies for a patient presenting with colchicine poisoning include complete blood count, glucose, electrolytes, renal and hepatic function tests, coagulation tests, creatine kinase, calcium, phosphorus, magnesium, arterial blood gases, chest X-ray, urinalysis, and continuous ECG monitoring.[17,33,41,47,106,107] Troponin, fibrinogen, fibrinogen split products, and echocardiography should be considered depending upon the clinical picture.[56,84,87,89,96,106] A pregnancy test is recommended in females. In the presence of organ dysfunction, a hematology blood smear displaying toxic vacuolation, gross dysplasia, and nuclear karyorrhexis should alert clinicians to possible colchicine poisoning.[35] Laboratory parameters should be serially monitored to detect possible delayed toxicity. Colchicine plasma concentrations may be measured by liquid chromatography-mass spectrometry, HPLC, and radioimmunoassay. However, they are neither readily available in the clinical setting, nor useful for the management of acute poisoning because there is no established correlation to severity of illness.[95,106,107]

Management

The mainstays of treatment consist of prompt recognition of colchicine poisoning, with, if possible, determination of the dose ingested or administered, early gastrointestinal decontamination, and aggressive supportive care. Management may be difficult if multi-organ failure develops.

In early (i.e., 1–2 h after ingestion) presentations of large ingestions, efforts to remove any remaining colchicine from the gastrointestinal tract by gastric lavage followed by activated charcoal should be attempted.[90] Large amounts of the drug have been found in the stomach 24 h after ingestion,[83] thus the use of activated charcoal may be considered even in late presentation. Enhanced elimination with multi-dose activated charcoal (MDAC) should be considered because of colchicine's enterohepatic re-circulation[17] and in cases of ingestion of colchicine-containing plants.[84] Although the efficacy of MDAC in managing colchicine poisoning has not been systematically studied, its use should be considered in patients with potentially serious or lethal ingestions. In case of vomiting, anti-emetics can be given to control emesis and facilitate activated charcoal administration. Paralytic ileus, which can develop as a complication of colchicine poisoning, may complicate the use of MDAC.[84,90] Extracorporeal elimination (e.g., hemodialysis and hemoperfusion) is ineffective mainly because of the large volume of distribution of colchicine.[99,108]

After decontamination, treatment is mainly supportive.[30] Sudden malignant arrhythmias and death have been reported in colchicine poisoning, and symptomatic patients or those

with confirmed ingested toxic doses should be monitored in an intensive care unit. Continuous monitoring of vital signs, ECG, and serial hematological and biochemical assessments is warranted. Treatment includes judicious administration of IV fluids, correction of electrolyte and acid–base balance, vasopressor drugs, antiarrhythmics, blood products, and mechanical ventilation.[30] Broad-spectrum antibiotics should also be given if a secondary infection is suspected or the patient is febrile.[47] Granulocyte colony-stimulating factor should be considered if there is leukopenia and is thought to accelerate production of neutrophils within the bone marrow and prevent development of septicemia.[47,109]

Effective experimental treatment with colchicine-specific Fab fragment antibodies was reported in a single adult patient with severe colchicine poisoning.[38] Positive hemodynamic effects were quickly noted, although bone marrow suppression did not significantly improve. Ultimately, the patient survived a large (60 mg) overdose. Colchicine-specific Fab fragments consist of the light chain and variable region of the heavy chain of antibodies derived from goats immunized with a conjugate of colchicine and serum albumin.[110] *In vitro* studies have shown that colchicine-specific antibodies restore the activity of tubulin inhibited by colchicine.[111] Their mechanism of action in the clinical setting is similar to that of digoxin-specific Fab fragment antibodies; both bind to the target drug allowing its redistribution into the extracellular space and intravascular compartment, and thus the removal of substantial amounts from peripheral tissues.[33,111,112] The high affinity of the Fab fragment antibodies to colchicine prevents the drug from binding to other peripheral sites. Presently, this treatment is not commercially available.

Conclusions

Colchicine poisoning is relatively uncommon, but potentially severe, and has a high mortality rate. It may easily be overlooked because presenting gastrointestinal manifestations may resemble other systemic diseases. Aggressive supportive treatment, including granulocyte colony-stimulating factor when appropriate, is required to manage colchicine's toxic effects. Specific therapy with Fab fragment antibodies seems to be effective but, unfortunately, is not commercially available at present.

Declaration of interest

The author reports no declarations of interest. The authors alone are responsible for the content and writing of this paper.

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