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PRACTICAL PEARL

Vomiting, Diarrhea, and Sudden Death With Recent Southeast Asian Travel

Fatal Colchicine Toxicity

Roger W. Byard, Peter C. Stockham, and John D. Gilbert

Forensic Science SA, Adelaide, Australia

Address for correspondence and reprints:

Roger W. Byard
Forensic Science SA,
21 Divett Place,
Adelaide 5000, Australia
E-mail:
byard.roger@saugov.sa.gov.au

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Abstract

A 41-year-old male was referred for autopsy from a hospital with a diagnosis of sepsis of uncertain etiology. As he had recently been attached to a military base in Southeast Asia, and had only just returned home, there was considerable concern that an unknown infectious agent may have been involved, which would necessitate screening of coworkers and contacts, with possible quarantine of the facilities where he had been working. His clinical history included a day of vomiting and diarrhea. Despite rehydration and antibiotic therapy, he died within hours of hospitalization. His only past medical history was of gout, for which he was prescribed allopurinol. At autopsy there was evidence of multiorgan failure but no focal sepsis. Postmortem microbiological tests including blood cultures, lung swab, colonic fecal culture, and a small intestinal swab were negative. Histological examination of small intestinal mucosa demonstrated numerous mitotic figures, which, in concert with the presentation, raised the possibility of colchicine toxicity. Subsequent reinterview of family members confirmed that the deceased had ingested an unknown quantity of colchicine on the day prior to his illness and toxicological evaluation demonstrated a toxic/potentially lethal level of 0.05 mg/L of colchicine in the blood. Death was therefore attributed to colchicine toxicity and not to occult sepsis. This case clearly demonstrates that causes of gastrointestinal illness other than sepsis need to be considered when patients have presented with vomiting and diarrhea. There may also be considerable public health implications if a death is incorrectly attributed to sepsis and then a specific infectious agent is not identified. Maintaining a broad approach to diagnostic possibilities is essential if forensic practitioners are to maintain a useful role in the investigation of unexpected deaths.

Key Words: Forensic pathology; colchicine; vomiting; diarrhea; death; travel.

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INTRODUCTION

Forensic pathologists are continually confronted with cases in which there is limited or inaccurate history. In the following report a 41-year-old man presented with symptoms and signs of sepsis following overseas travel. The autopsy investigation is reported to demonstrate the importance of combined microbiological, toxicological, and histological study in such cases where there may not be a clear-cut indication of the cause of death. The case also shows that the medical history, even in supposedly well-evaluated hospital cases, may be inadequate with failure to document important information concerning prescribed medications.

CASE REPORT

A 41-year-old white male presented to a local hospital with a one day history of vomiting and diarrhea. He had a history of recently working at a military base in Malaysia, returning shortly before this episode. His only past medical history was

of episodic gout reportedly successfully treated with allopurinol. On presentation he was dehydrated with anuria but afebrile. A diagnosis of acute renal failure secondary to sepsis was made. Rehydration was commenced and a chest radiograph was performed that was unremarkable. Elevation of his white blood cell count with a neutrophil count of 17.06×10^9/L (59%) and a shift to the left with toxic changes were in keeping with infection, although no primary focus could be identified. Microbiological screening was therefore undertaken and he was commenced on broad spectrum antibiotics. Approximately 6 hours after hospital admission, his clinical condition deteriorated with cardiorespiratory arrest that did not respond to resuscitative attempts. The clinical diagnosis was of presumed sepsis. Given his recent history of travel to Southeast Asia, there was considerable concern as to the nature of the possible infectious agent, particularly as he had been working on a military base.

At autopsy, there was evidence of multiorgan failure with congestion and edema of the lungs with bilateral straw-colored pleural effusions and ascites. There was also significant cardiomegaly of uncertain etiology (heart weight 625 g; body weight 106 kg). However, there was no histologic evidence of cardiomyopathy and the finding was regarded as being incidental to the cause of death given subsequent developments. There were no other underlying organic diseases that may have caused or contributed to death and there was no evidence of trauma, apart from medical intervention. Specifically, there was no evidence of pneumonia or other inflammatory/infectious conditions.

Although there was no history of colchicine ingestion, extensive tissue sampling was undertaken at autopsy given the similarity of the presenting symptoms and signs to colchicine toxicity, the failure to detect any infectious organisms on the results of preliminary screening, and the history of gout. Histological examination of tissues revealed features characteristic of colchicine toxicity, with widespread metaphase arrest resulting in numerous mitotic figures observed mainly in autolytic mucosa of the gastrointestinal tract (Fig. 1).

A request was therefore made by the examining pathologist for reinterview of family members, following the histologic findings, where it was revealed that the deceased had in fact possessed colchicine and had been seen taking an unspecified amount on the day before his death. He was known to take greater amounts than were prescribed when he was aware that an attack was imminent. Unfortunately, his partner had already discarded all of his medications and so calculation of the amount taken from remaining empty containers/packets was not possible. However, toxicological evaluation on postmortem blood subsequently confirmed the presence of a toxic/potentially lethal level of 0.05 mg/L of colchicine (the level on hospital admission blood was 0.03 mg/L). The only other findings were of a subtherapeutic level of oxypurinol (4.6 mg/L), a metabolite of allopurinol. Postmortem microbiological studies including aerobic and anerobic blood cultures, lung swab, colonic fecal culture, and a small intestinal swab did not show significant growth.

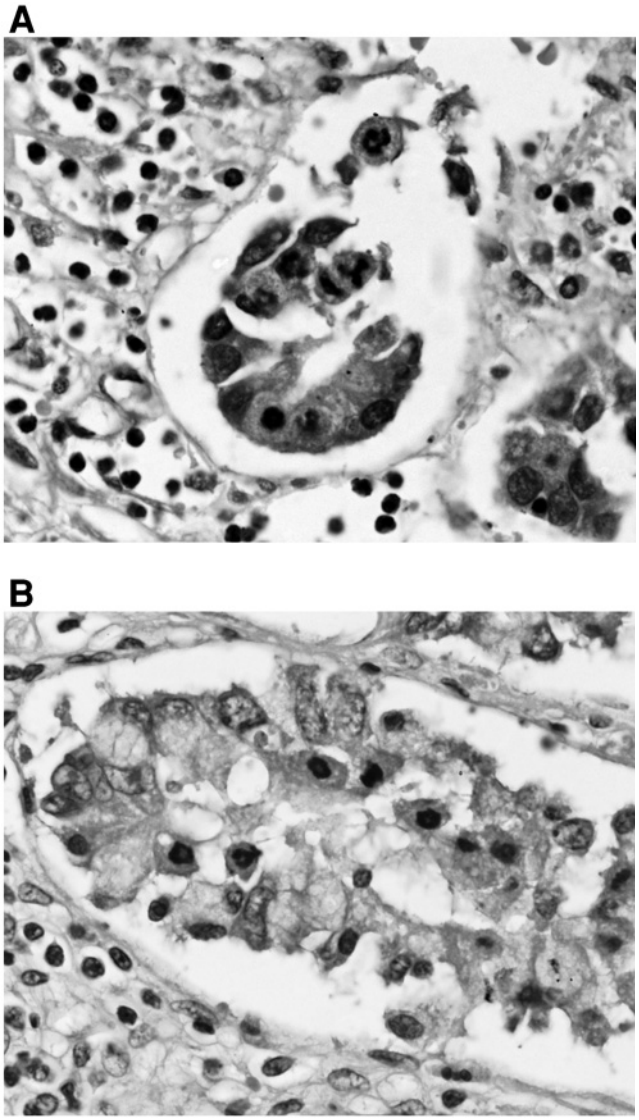

Fig. 1. Numerous mitotic figures present in poorly preserved small **(A)** and large **(B)** intestinal mucosa (Hematoxylin & Eosin x400).

Given the circumstances of death and the histological and toxicological findings, death was attributed to colchicine toxicity.

DISCUSSION

Given the history of recent overseas travel, with a rapid onset of diarrhea and vomiting, it is perhaps not surprising that attending medical staff suspected an infectious cause for the presentation of the deceased. Unfortunately, colchicine may produce similar clinical features to sepsis, with vomiting and diarrhea *(1,2)*. In the present case, the clue to the diagnosis lay in the negative laboratory tests for sepsis and the history of gout. Despite no documentation of prescribed colchicine, this was revealed on subsequent interview of family members

following the finding of characteristic histological features of arrested metaphases in intestinal mucosal cells. Awareness of the manifestations of colchicine toxicity is perhaps slightly higher at our institution than elsewhere following a previous case involving the unexpected death of a 39-year-old man with similar presenting features, who died approximately 2 days after ingesting a bolus dose of the drug *(1)*.

Colchicine is used as an anti-inflammatory agent in the treatment of arthritis and particularly gout, and derives from the bulb of the meadow saffron (autumn crocus). It has a variety of actions at the cellular and subcellular level, blocking cell microtubular function, interfering with collagen deposition, inhibiting fibroblast proliferation, and interfering with white cell chemotaxis *(3)*.

The clinical manifestations of acute colchicine poisoning usually begin after a latent period of 4 to 12 hours and are initially characterized by gastrointestinal symptoms and signs with diarrhea and hypovolemic shock. The peripheral leukocytosis that occurs at this stage, as in the reported case, may be confused with sepsis. As there is no specific treatment for colchicine toxicity, early diagnosis is imperative, because gastric lavage and activated charcoal are required to remove as much of the drug as possible from the stomach and to prevent absorption. Once in the system there is no antidote and hemodialysis is ineffectual *(2–4)*. Multiorgan failure occurs with acute renal failure, liver failure, neurological disturbances, cardiac failure, respiratory failure secondary to adult respiratory distress syndrome, and neuropathy affecting respiratory muscles. Progressive weakness and coma may proceed to death within several days *(2,5,6)*. A lethal outcome may occur even with relatively low doses *(7)*.

Fatal poisoning with colchicine has occurred following intravenous administration for acute gout *(8)* and may also occur accidentally if there has been ingestion of wild plants. For example, cases have been reported where deaths have followed ingestion of meadow saffron instead of wild garlic *(4,9)*. Cases have been reported where deliberate overdose has occurred in suicides *(10–12)*.

Characteristic histologic findings may be extremely useful in suggesting the diagnosis to assist in directing subsequent police/medical inquiries and in focusing toxicological evaluation. The finding of increased numbers of mitotic figures derives from a direct effect of colchicine on the prevention of the polymerisation of tubulin, resulting in failure of spindle formation and thus prevention of normal chromosomal aggregation and replication *(4,13)*.

It is important at the time of autopsy in suspected cases to sample as many tissues as possible, because the presence of increased mitotic figures appears to vary among tissues. In addition, postmortem tissue and cellular autolysis may reduce the usefulness of histological evaluation of certain organs. In the current case, increased mitoses were most obvious in small intestinal mucosal cells, compared to our previously reported case where mitoses were most easily identified in the mucosa of the esophagus and bronchioles *(1)*. In addition to manifestations within the gastrointestinal tract, increased mitoses have been found in lymph nodes, liver, endometrium, bone marrow, kidneys, and bladder *(14,15)*.

Toxicological evaluation may be difficult in cases of suspected colchicine poisoning as the half-life in blood may be as short as 19 minutes *(3)* with significant excretion into bile lowering blood levels markedly, even after massive overdose *(10)*. This means that hospital admission bloods may be required, particularly if a number of days have elapsed between ingestion and death. Excretion of the drug may be delayed if there is pre-existing liver disease, which may also contribute to a poorer prognosis *(6)*.

The importance of considering toxic causes of gastrointestinal illness rather than limiting the differential diagnosis to infectious etiologies is clear. Therapy is entirely different and many toxic agents require early diagnosis and treatment if a cure is to be achieved. The public health implications of assuming a death to be septic and then being unable to find a specific infectious agent are also considerable in terms of both resources and contact anxiety. In the reported case, there was no need for screening of fellow workers or hospital staff, or quarantine of the base where the deceased had been stationed for a 2-week period close to his death, activities that were being considered before establishment of the cause of death. Given that the recent outbreak of severe acute respiratory syndrome has further concentrated attention on infectious disease, maintaining an open mind is important when initially evaluating cases of possible sepsis.

Educational Message

1. Causes of gastrointestinal illness other than sepsis need to be considered when there are histories of vomiting and diarrhea.
2. Numerous mitotic figures on microscopy should raise the possibility of colchicine toxicity.
3. The clinical manifestations of acute colchicine toxicity usually begin after a latent period of 4 to 12 hours and are initially characterized by gastrointestinal symptoms and signs with diarrhea and hypovolemic shock.
4. It is important at the time of autopsy in suspected cases to sample as many tissues as possible, as the presence of increased mitotic figures appears to vary among tissues.

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