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Colchicine-associated Ring Mitosis in Liver Biopsy and Their Clinical Implications

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Abstract

Colchicine is an alkaloid with antimitotic activity used to treat a variety of medical conditions. Colchicine toxicity can result in multiorgan failure and death. In recent years, the histopathologic features of colchicine toxicity in various organs that is, gastrointestinal tract, kidneys, salivary glands, muscle, and skin have been described. However, the histopathologic manifestations of colchicine in the liver have not been reported. We present the case of a 54-year-old man with transfusion acquired chronic hepatitis C and longstanding gout managed with colchicine. A liver biopsy performed showed changes consistent with chronic hepatitis C along with many scattered mitoses arrested in metaphase in the hepatocytes that have been referred to as “ring” mitoses. The current liver biopsy was compared with the biopsy from 7 years ago, which appeared similar, however, ring mitoses were absent. Ring mitosis have been associated with colchicine-mediated tissue injury in various other sites, and their presence is felt to represent colchicine-induced liver injury in this case.

Keywords

colchicine; ring mitotic figures

Colchicine is a lipid-soluble alkaloid derived from the bulb of the autumn crocus, *Colchicum autumnale*, or meadow saffron and it has been used for centuries as an anti-inflammatory agent in the treatment of arthritis. The biologic effects of colchicine vary widely and include interference with leukocyte chemotaxis, microtubule function, extracellular collagen deposition, and fibroblast proliferation.¹ Although traditionally used in the treatment of gout² and familial Mediterranean fever, colchicine has been more widely used in recent times in the treatment of many other disorders.^{3–7}

Studies have shown that colchicine undergoes extensive metabolism in the liver, and then, biliary and renal excretion.^{8,9} Thus, liver disease may predispose to its toxicity. Patients with compromised hepatic and/or renal function must be closely monitored as reduced clearance of standard dosages of colchicine may result in toxic levels and in some cases death. There is no specific treatment for colchicine toxicity. The outcome is most favorable with early diagnosis and treatment. Although the occurrence of colchicine hepatotoxicity

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and its contributing factors have been well described in several case reports, histopathologic changes as a result of colchicine therapy in the liver have not been reported to date.

CASE REPORT

We present the case of a 54-year-old man with chronic hepatitis C, acquired 15 years ago via blood transfusion. He has been taking oral colchicine (>10 y) for long standing gout. He underwent a cadaveric renal transplant in 1991 for end stage renal disease. Before renal transplantation he had a liver biopsy that revealed mild chronic hepatitis C with grade I inflammation and stage 2 fibrosis (Batts and Ludwig staging system¹⁰), for which he was not treated. His medical history is also significant for anemia as a consequence of his renal disease, resections for multiple squamous cell carcinomas and mild glaucoma. Besides colchicine, his current medications include labetalol, enalapril, lasix, probenecid, kaletra, prednisone, genvir, cosopt, and captopril.

The patient has been on 0.6 mg of colchicine once a day and felt well in general. He had no nausea, vomiting, abdominal discomfort, peripheral edema, confusion, jaundice, fever, or chills. An attempt to replace colchicine with allopurinol was prompted by his developing loose stools; however, he developed an allergic skin rash with allopurinol leading to its discontinuation. In the past, his transaminases have been mildly elevated with aspartate aminotransferase ranging between 43 and 58 U/L and alanine aminotransferase ranging between 45 and 88 U/L. Currently, he has no hematologic evidence of colchicine toxicity such as granulocytopenia, pancytopenia, immature leukocytes, or thrombocytopenia. On examination, he had no stigmata of chronic liver disease. Physical examination was significant for peripheral edema, dry eyes, and severe tophaceous gout with tophi on both elbows and diffusely on his hands. His most recent aspartate aminotransferase was 50 U/L (normal 0 to 35 U/L), alanine aminotransferase was 50 U/L (normal 0 to 35 U/L), and hemoglobin was 10.2 g/dL.

A liver biopsy was obtained at this time to document any disease progression and changes seen were largely similar to the previous biopsy with regard to chronic hepatitis C. The inflammatory grade was similar to the previous biopsy. Few scattered acidophil bodies were noted throughout the biopsy, although the difference in the number of acidophil bodies in the 2 biopsies was minimal, if any. Focal suggestion of early bridging fibrosis was noted, suggestive of possibly mild progression, however, variation owing to sampling cannot be excluded. Mild macrovesicular steatosis was also noted. There was no evidence of hepatic siderosis or α -1 antitrypsin type globules. The most discriminating feature was the presence of scattered mitotic figures arrested in metaphase in the hepatocytes (Fig. 1). The cells showed condensed chromatin in a ring form in the center of the cell ("ring" mitotic figures). Approximately, one ring mitosis was seen every 5 high-power field. The liver biopsy performed 7 years ago on review failed to show any ring mitoses, although the patient was on colchicine at that time. Owing to developing diarrhea a possibility of colchicine toxicity is suspected, however, he cannot be taken off the medication owing to his chronic gout, and close monitoring of his gastrointestinal symptoms and liver enzymes has been undertaken.

DISCUSSION

At a cellular level, colchicine is an antimetabolic agent that inhibits mitosis by preventing the polymerization of tubulin,^{11,12} a constituent microtubule protein, thereby disturbing those processes dependent on microtubule function such as cell motility, intracellular movement, cell polarity, and mitosis.¹³ This results in a failure of spindle formation, thus, preventing normal chromosomal movement and replication. Consequently, the toxicities of colchicine are most apparent in tissues with a high mitotic rate such as hair follicles, bone marrow, and

gastrointestinal epithelium. The histopathologic features of colchicine toxicity in biopsies from the gastrointestinal tract have recently been described, with epithelial pseudostratification, loss of cellular polarity, and increased number of ring mitotic figures.¹⁴ The most obvious changes occur in the gastric antrum and duodenum with relative sparing of the fundic and body mucosa.¹⁴ Ki-67 staining reveals widening of the proliferative region of the gut mucosa. Other studies have also described increased mitotic figures in the bone marrow, lymph nodes, endometrium, bladder, and renal tubular epithelium.^{14,15} Autopsy studies of colchicine-toxic patients describe arrested mitosis in lymph nodes, spleen, colon, small intestine, esophagus, kidney, urinary tract, and respiratory tract.^{15–20} In 1936, these arrested mitoses were dubbed colchicine figures,²¹ a term which was widely used in the literature.^{21–24}

The pathogenesis of epithelial injury as a result of colchicine seems to be caused by a loss of cellular renewal.²⁵ Atrophy of proliferative epithelium is hypothesized to be owing to extensive mitotic arrest. On the other hand, sometimes as the effects of colchicine wear off, a duration of intense compensatory proliferation leads to the hyperplasia of epithelial tissues. The histologic features of increased mitotic figures and loss of polarity along with epithelial pseudostratification may mimic epithelial dysplasia. The lack of nuclear hyperchromasia or atypia and general preservation of architecture helps to distinguish colchicine toxicity from genuine dysplasia. The differential diagnosis to be kept in mind while looking for apoptosis associated with colchicine are chronic nonsteroidal anti-inflammatory drug use, viral infections, and graft versus host disease.⁴ In our case, one could ask if the patient has colchicine toxicity or the findings merely represent a histologic marker of use of this drug, and a conclusive proof is lacking. Inability to withdraw the medication makes it difficult to conclude that liver enzyme abnormalities are due to colchicine and not merely chronic hepatitis C. However, owing to strong evidence that similar changes in other organs and tissues represent colchicine toxicity, we believe these histologic changes to represent colchicine hepatotoxicity. Increasing loose stools also supports this interpretation. It is also recognized that although many patients are on colchicine, finding ring mitosis is not a common finding in tissue biopsies in practice. It is also likely that as the cell proliferation increases in various tissues in patients taking colchicine, the chances of finding cells arrested in metaphase with ring mitosis also increases, and in some cases the cell proliferation may be stimulated by drug injury. Increased number of cells arrested in metaphase mitoses owing to colchicine during tissue regeneration may contribute to drug toxicity or accentuate tissue injury owing to other disorders, for example, chronic hepatitis C in this case. Pathologists should carefully look for this finding in liver biopsies of patients on colchicine as the findings could be subtle. Clearly, more studies are needed to elucidate the clinical significance of “ring mitoses” in this setting.

In summary, distinct morphologic features such as arrested metaphase mitoses (ring mitoses) and apoptosis may be seen in liver biopsy in patients taking colchicine and possibly indicate hepatotoxicity of the drug. Because treatment options available today are largely supportive and toxicity could be fatal, early recognition of the histomorphologic features of colchicine toxicity are important in the management of such patients.

References

1. Levy M, Spino M, Read SE. Colchicine: a state-of-the-art review. *Pharmacotherapy*. 1991; 11:196–211. [PubMed: 1862011]
2. Roberts WN, Liang MN, Stern SH. Colchicine in acute gout: reassessment of risks and benefits. *JAMA*. 1987; 257:1920–1922. [PubMed: 3820512]
3. Ben-Chetrit E, Levy M. Colchicine: 1998 update. *Semin Arthritis Rheum*. 1998; 28:48–59. [PubMed: 9726336]

4. Sullivan TP, King LE Jr, Boyd AS. Colchicine in dermatology. *J Am Acad Dermatol.* 1998; 39:993–999. [PubMed: 9843014]
5. Simons RJ, Kingma DW. Fatal colchicine toxicity. *Am J Med.* 1989; 86:356–357. [PubMed: 2919622]
6. Emerson, B.; Klippel, JH.; Dieppe, P. *The Management of Gout Rheumatology.* 2. Philadelphia: Mosby; 1998. p. 15.1-15.8.
7. Insel, P. Analgesic-antipyretic and antiinflammatory agents and drugs employed in the treatment of gout. In: Hardman, JG.; Limbard, LE.; Molinoff, PB., et al., editors. *The Pharmacological Basis of Therapeutics.* 9. New York, NY: McGraw Hill; 1996. p. 633-635.
8. Ferron GM, Rochdi M, Jusko WJ, et al. Oral absorption characteristics and pharmacokinetics of colchicine in healthy volunteers after single and multiple doses. *J Clin Pharmacol.* 1996; 36:874–883. [PubMed: 8930773]
9. Leighton SA, Bay MK, Maldonado AL, et al. Colchicine clearance is impaired in alcoholic cirrhosis. *Hepatology.* 1991; 14:1013–1015. [PubMed: 1959847]
10. Batts KP, Ludwig J. Chronic hepatitis; An update on terminology and reporting. *Am J Surg Pathol.* 1995; 19:1409–1417. [PubMed: 7503362]
11. Rieder CL, Palazzo RE. Colcemid and the mitotic cycle. *J Cell Sci.* 1992; 102:387–392. [PubMed: 1506421]
12. Stapczynski JS, Rothstein RJ, Gaye WA, et al. Colchicine overdose: report of two cases and review of the literature. *Ann Emerg Med.* 1981; 10:364–369. [PubMed: 7018330]
13. Panda D, Daijo JE, Jordan MA, et al. Kinetic stabilization of microtubule dynamics at steady state in vitro by substoichiometric concentrations of tubulin-colchicine complex. *Biochemistry.* 1995; 34:9921–9929. [PubMed: 7632691]
14. Iacobuzio-Donahue CA, Lee EL, Abraham SC, et al. Colchicine toxicity: distinct morphologic findings in gastrointestinal biopsies. *Am J Surg Pathol.* 2001; 25:1067–1073. [PubMed: 11474292]
15. Brown WO, Seed L. Effect of colchicine on human tissues. *Am J Clin Pathol.* 1945; 15:189–195.
16. Heaney D, Derghazarian CB, Pineo GF, et al. Massive colchicine overdose: a report on the toxicity. *Am J Med Sci.* 1976; 271:233–238. [PubMed: 946740]
17. Davies HO, Hyland RH, Morgan CD, et al. Massive overdose of colchicine. *Can Med Assoc J.* 1988; 138:335–336. [PubMed: 3338005]
18. Gilbert JD, Byard RW. Epithelial cell mitotic arrest: a useful postmortem histologic marker in cases of possible colchicine toxicity. *Forensic Sci Int.* 2002; 126:150–152. [PubMed: 12084492]
19. Simons RJ, Klingma DW. Fatal colchicine toxicity. *Am J Med.* 1989; 86:356–357. [PubMed: 2919622]
20. Finger JE, Headington JT. Colchicine-induced epithelial atypia. *Am J Clin Pathol.* 1963; 40:605–609. [PubMed: 14100663]
21. Ludford RJ. The action of toxic substances upon the division of normal and malignant cells in vitro and in vivo. *Arch Exp Zellforsch.* 1936; 18:411.
22. Stemmermann GN, Hayashi T. Colchicine intoxication. A reappraisal of its pathology based on a study of three fatal cases. *Hum Pathol.* 1971; 2:321–332. [PubMed: 5095674]
23. Klintschar M, Beham-Schmidt C, Radner H, et al. Colchicine poisoning by accidental ingestion of meadow saffron (*Colchicum autumnale*): pathological and medicolegal aspects. *Forensic Sci Int.* 1999; 106:191–200. [PubMed: 10680067]
24. Sannohe S, Mamakino Y, Kita T, et al. Colchicine poisoning resulting from accidental ingestion of meadow saffron (*Colchicum autumnale*). *J Forensic Sci.* 2002; 47:1391–1396. [PubMed: 12455670]
25. Stahl N, Weinberger A, Benjamin D, et al. Fatal colchicine poisoning in a boy with familial Mediterranean fever. *Am J Med Sci.* 1979; 278:77–81. [PubMed: 484593]

FIGURE 1.
High-power view of the liver biopsy (hematoxylin and eosin stain) showing 2 hepatocytes with mitoses arrested in metaphase (ring mitosis).