

Colchicine-Induced Hepatotoxicity

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ABSTRACT

Drug-induced injury (DILI) is a frequent cause of abnormal liver tests and a leading cause of liver failure in the United States. Colchicine has long been used as a systemic anti-inflammatory agent for treatment of gout by inhibiting mitotic activity and neutrophil function. We present the first case of colchicine-induced hepatotoxicity, supported by histopathologic findings characteristic of colchicine-induced injury and resolution of liver enzyme abnormalities after its discontinuation. Colchicine-associated DILI has implications for the evaluation of patients with abnormal liver tests and gout, especially for patients with alcoholism and non-alcoholic fatty liver disease, in whom there is an increased incidence of gout.

INTRODUCTION

Drug-induced liver injury (DILI) accounts for 10% of all episodes of acute hepatitis and is the most common cause of liver failure in the United States.^{1,2} DILI can cause either hepatocellular or cholestatic injury, and its severity ranges from asymptomatic mild elevations in liver tests, to nonspecific symptoms with nausea, anorexia, and fatigue, and even to fulminant hepatic failure with jaundice and hepatic encephalopathy. Proposed mechanisms of DILI include direct cellular injury and immune-mediated injury. Most cases subside after cessation of the drug, which serves as an important diagnostic and therapeutic aide.³

Colchicine is used as a treatment for gout, and the biologic effects of colchicine are based on its ability to bind to tubulin. Colchicine forms a tight complex with tubulin and induces a conformational change in the protein that inhibits its polymerization into microtubules, thereby leading to mitotic arrest in metaphase and disruption of cellular division.⁴ Its anti-inflammatory effect is attributed to its ability to disrupt neutrophil microtubules and inhibit neutrophil migration and adhesion.⁵ Colchicine demonstrates the greatest anti-mitotic activity on rapidly dividing tissues, so toxicity initially presents with gastrointestinal (GI) symptoms, but patients can develop bone marrow hypoplasia, cardiac arrhythmias, cardiovascular collapse, respiratory distress, and shock, which can lead to multisystem organ failure.⁶⁻⁸ Colchicine has only infrequently been associated with hepatotoxicity. It has usually been associated with cases of overdose in which the hepatic injury has been self-limited and overshadowed by the other toxicities.

CASE REPORT

A 41-year-old, non-obese man was started on 0.6 mg oral colchicine and allopurinol daily for treatment of chronic gout. Liver tests immediately prior to starting therapy were not available, but such tests were noted to be mildly abnormal at 6 months after starting colchicine and remained so after discontinuing allopurinol. The tests were remarkable for aspartate aminotransferase (AST) 50 IU/L, alanine aminotransferase (ALT) 47 IU/L, and alkaline phosphatase 76 IU/L. Serologic evaluation was remarkable for anti-mitochondrial antibody 74.9. Anti-nuclear antibody, anti-smooth muscle antibody, liver-kidney microsomal antibody, celiac serologies, and immunoglobulin levels, as well

ACG Case Rep J 2017;4:e120. doi:10.14309/crj.2017.120. Published online: November 22, 2017.

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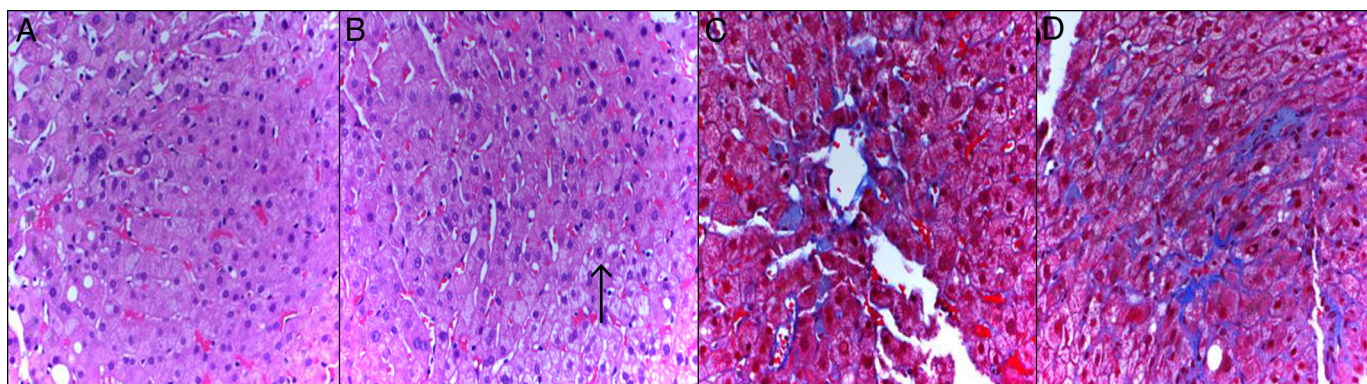


Figure 1. (A) Histological features of liver biopsy, showing significant anisonucleosis, mild liver cell plate disarray, loss of nuclear polarity, hepatocytes and glycogenated nuclei, and focal macrovesicular steatosis (hematoxylin and eosin stain, 40 \times magnification). (B) Frequent mitotic figures (arrow) (hematoxylin and eosin stain, 40 \times magnification). (C) Trichrome stain highlighting peri-centrovenular fibrosis (40 \times magnification). (D) Trichrome stain highlighting peri-sinusoidal/peri-hepatocellular fibrosis (40 \times magnification).

as α -1-antitrypsin and ferritin levels were normal. M2 subtype was not measured, but the patient was not taking any antibiotics, and, as described below, histopathology was inconsistent with primary biliary cirrhosis (PBC). Physical examination was unremarkable without stigmata of chronic liver disease. Abdominal ultrasound was normal. Liver biopsy was remarkable for focal hepatocytes with glycogenated nuclei, 1% macrovesicular steatosis, occasional ceroid macrophages, and significant anisonucleosis with enlarged nuclei, multiple nucleoli, and frequent mitotic figures (Figure 1). This is indirectly suggestive of mitotic arrest, which is colchicine's mechanism of action. The liver biopsy did not have features suggestive of primary biliary cholangitis or granulomatous features suggestive of allopurinol-induced liver injury. After discontinuing colchicine, liver tests normalized within 3 weeks (AST 33 IU/L, ALT 40 IU/L).

DISCUSSION

The abnormal liver tests in our patient can be attributed to colchicine-associated liver injury due to its resolution after colchicine was discontinued and other etiologies were excluded. Although the presence of anti-mitochondrial antibody raised the possibility of PBC, the liver test pattern was hepatocellular rather than cholestatic, the immunoglobulin M (IgM) level was normal, and the liver biopsy lacked features of this condition. Nearly half of newly detected anti-mitochondrial antibodies in clinical practice do not lead to PBC, and there was no clinical evidence to suggest that this patient had PBC.⁹ Although allopurinol is associated with minor liver test abnormalities and has been linked to acute liver injury with features of a hypersensitivity reaction, liver tests in our patient remained elevated despite discontinuing allopurinol, and the histopathology was inconsistent with the granulomatous disease characteristic of allopurinol-induced liver injury.¹⁰

The histopathologic changes observed in the liver biopsy were consistent with colchicine's mechanism of action, in which

mitotic activity and cellular division is disrupted. These changes include anisonucleosis with enlarged nuclei, multiple nucleoli, and frequent mitotic figures, which is suggestive of mitotic arrest. These changes are similar to histological changes seen in GI, bronchiolar, and cardiac biopsies in patients with colchicine toxicity, which show endothelial cell injury, mitotic figures arrested in metaphase ("ring" mitoses), nuclear swelling, and loss of nuclear polarity.^{11,12}

The majority of cases of hepatotoxicity associated with colchicine are in the setting of multisystem organ failure with hepatic histologic findings consistent with sepsis.¹³ Reports of chronic colchicine hepatotoxicity are limited to 2 case reports of patients taking the agent for gout. Liver biopsy in a patient with chronic hepatitis C who had been taking colchicine for more than 10 years presented with mildly elevated liver tests and loose stools revealed "ring" mitotic figures that were not present on a previous biopsy 7 years earlier when he was also taking the agent.¹⁴ Colchicine is most toxic to highly proliferative tissues. It is unclear why ring mitoses were not initially present in this case and ours. One explanation is that it is a feature of only chronic toxicity. Results of liver tests after the discontinuation of colchicine were not reported in this case. In a second case, a patient with gout presented with transient loose stools, sub-acute painless jaundice, and elevated liver tests after taking 0.5 mg colchicine twice daily for 6 days, all of which gradually improved after discontinuing colchicine.¹⁵ A liver biopsy was not performed in this case.

When evaluating elevated liver tests in patients with gout, important considerations in the differential diagnosis include DILI (allopurinol, non-steroidal anti-inflammatory drug), and fatty liver disease. Alcohol abuse is a frequent causative factor for gout among those with regular alcohol use.^{16,17} Additionally, gout is an independent risk factor for non-alcoholic fatty liver disease (NAFLD).^{18,19} Given the increasing worldwide epidemic of NAFLD, it is anticipated that abnormal

liver tests associated with colchicine therapy in patients with fatty liver and gout will be more commonly encountered. Our case, which is the first biopsy-proven case of colchicine-induced hepatotoxicity, highlights the importance of considering colchicine-DILI in patients with abnormal liver tests and gout.

DISCLOSURES

Author contributions: CE Abbott wrote the manuscript. R. Xu edited the manuscript. SH Sigal edited the manuscript and is the article guarantor.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Received May 15, 2017; Accepted September 21, 2017

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