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CASE REPORT | LIVER

Severe Drug-Induced Liver Injury Due to Self-administration of the Veterinary Anthelmintic Medication, Fenbendazole

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ABSTRACT

Fenbendazole is an anthelmintic agent approved for veterinary applications. Even though it is not approved by the US Food and Drug Administration for human use, such use appears to be increasing due to the popularization of fenbendazole's potential anticancer effects by social media. We describe the first case of histologically confirmed severe drug-induced liver injury, hepatocellular pattern, associated with the self-administration of fenbendazole in a 67-year-old woman who presented with 2 weeks of jaundice. Liver function tests normalized in 3 months after the cessation of fenbendazole.

KEYWORDS: drug-induced liver injury; fenbendazole; hepatotoxicity; liver biopsy; liver function tests

INTRODUCTION

Fenbendazole is a benzimidazole anthelmintic widely used in animals.[1] Fenbendazole binds tubulin in parasites, and its applications include the treatment of pinworm infections in laboratory rodents and canine deworming.[2] It has also been reported to have antitumor effects, with a proposed mechanism overlapping with antineoplastic agents such as vinca alkaloids and taxanes.[3,4] The safety of fenbendazole has not been established in humans.[1] Despite the lack of safety and efficacy data, off-label human fenbendazole use for cancer has been promoted on social media. Several reports suggest potential hepatotoxicty for fenbendazole in humans. A clinical trial reported liver enzyme abnormalities with oxfendazole, an activated fenbendazole metabolite.[5] A case of probable mild drug-induced liver injury (DILI) associated with fenbendazole has been reported in a woman with lung cancer.[6] Moreover, human hepatotoxicity has been reported for the related benzimidazole medication, albendazole. Albendazole therapy has commonly been associated with mild and transient liver enzyme elevations (hepatocellular or mixed pattern) and rarely clinically apparent acute liver injury.[7]

We report the first histology-confirmed case of severe DILI due to fenbendazole in a female who was self-administering this agent for premalignant skin lesions.

CASE REPORT

A 67-year-old woman with a history of colon cancer status after hemicolectomy presented with 2 weeks of jaundice, nausea, anorexia, dark urine, and 2 days of a painful and pruritic rash. She had no history of liver disease. She reported drinking 2 glasses of wine daily. Her only reported medications were hormone replacement therapy with estrogen-progesterone-testosterone supplements for many years and recent cephalexin administration for 2 days for a presumed urinary tract infection due to dark urine, which was stopped 4 days before presentation. The rash began 2 days after antibiotics. On physical examination, she was alert and oriented, icteric, and had a maculopapular rash over her back and abdomen. Laboratory studies revealed a total bilirubin of

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13.3 mg/dL (direct 8.1 mg/dL, indirect 5.2 mg/dL), aspartate transaminase (AST) of 1,869 U/L, alanine transaminase (ALT) of 2,600 U/L, alkaline phosphatase of 141 U/L, and international normalized ratio (INR) of 1.6. Viral hepatitis panel was negative.

Workup was sent for a broad differential including autoimmune hepatitis, ischemic hepatitis, Budd-Chiari syndrome, Wilson disease, hemochromatosis, malignancy, etc., which later returned negative. Empiric therapy with N-acetylcysteine was initiated due to the unknown etiology of acute liver injury. Cholestyramine was started for hyperbilirubinemia and pruritus, and vitamin K for coagulopathy. Ultrasound showed a right hepatic lesion with internal vascularity. Magnetic resonance imaging revealed a benign hemangioma. No biliary or vascular obstruction was present.

AST and ALT levels started to decline, but bilirubin continued to rise. Upon further inquiry, she admitted to taking fenbendazole for the past year. She had been self-administering three 1 g packets of fenbendazole granules thrice weekly for a precancerous skin lesion, after hearing about fenbendazole's potential anticancer benefits from social media. Her last reported use was 4 days before admission. Bilirubin peaked at 24 mg/dL. There was no hepatic encephalopathy. A liver biopsy was performed, and budesonide was started. The biopsy demonstrated centrilobular hepatocyte injury with broad zones of necrosis. A lymphocyte-predominant portal inflammatory infiltrate was seen. These findings were consistent with DILI (Figure 1). Serum transaminases decreased by more than 50% by day 7 of hospitalization, and she was discharged. On outpatient follow-up 1 month later, liver function tests improved to a bilirubin of 4.3 mg/dL, AST of 78 U/L, ALT of 86 U/L, and INR of 1.1. These tests completely normalized within 3 months.

DISCUSSION

Fenbendazole, like some antineoplastic agents, acts by inhibiting polymerization of tubulin subunits that form microtubules, which are part of the cytoskeleton.[3] This has led to multiple experimental studies, which have demonstrated the antitumor effects of fenbendazole.[4,8,9] However, its role in humans has not been confirmed due to the lack of clinical trial data.[6]

With reference to our patient, cephalosporins can cause minor liver function test (LFT) elevations, but severe liver injury is rare.[10] Oral cephalosporins, however, are known to cause nonimmediate reactions including maculopapular rashes.[11,12] The rash exhibited by our patient was thus credited to recent cephalexin administration. Estrogens can cause cholestatic liver injury which typically arises during the first few cycles of therapy but rarely after 6 months.[13] Liver enzyme elevations with androgenic steroid use are usually asymptomatic and self-limited.[14] Other than transient LFT elevations, estrogens and androgenic steroids can cause other hepatic complications including hepatic tumors and hepatic venous thrombosis (with estrogens), but the characteristic pattern is bland intrahepatic cholestasis with little inflammation or necrosis on biopsy, contrary to our case.[13,14] Progestins can lead to transaminase elevations which generally occur after 1–2 weeks of treatment without alkaline phosphatase or bilirubin changes.[15] Thus, these agents were unlikely to have precipitated her severe acute liver injury.

A score of 9 points on the Roussel Uclaf Causality Assessment Method scale indicated a high probability of causation of DILI by fenbendazole.[16] As per the DILI Network scale for liver injury severity grading, our patient met the criteria for severe DILI (elevated ALT, total bilirubin $>$ 2.5 mg/dL, INR $>$ 1.5).[17] Biopsy findings compatible with severe DILI helped attain the

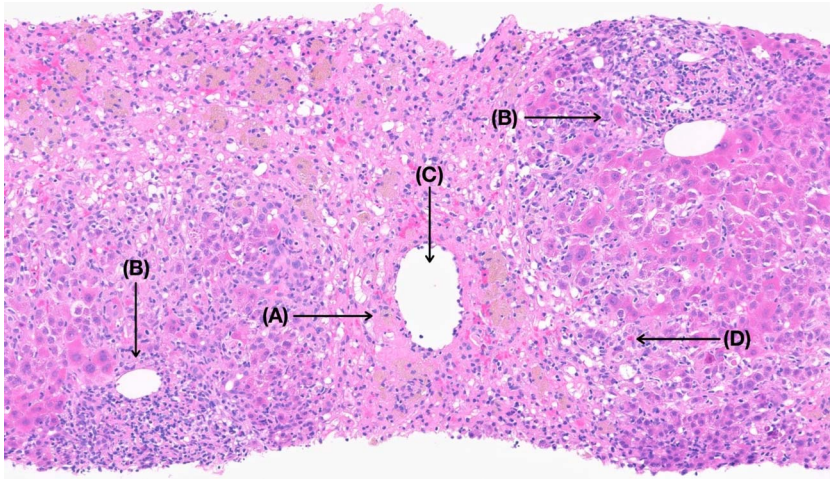

Figure 1. Hematoxylin and eosin-stained liver biopsy specimen (10× magnification) demonstrating pathologic features consistent with severe DILI: (A) centrilobular hepatocyte injury with necrosis, (B) portal triads with lymphocyte-predominant inflammatory infiltrates, (C) central vein, and (D) acidophil bodies.

diagnosis and exclude alternative diagnoses. Furthermore, LFTs normalized upon discontinuing fenbendazole. Although 1 case of mild DILI (elevated ALT, total bilirubin <2.5 mg/dL, no coagulopathy) probably caused by fenbendazole has been reported in a woman with non–small-cell lung carcinoma, it was not histologically confirmed and had a possible confounder of active programmed cell death ligand-1 inhibitor therapy, a known precipitant of immune-mediated hepatitis.[6,17] Hence, this is the first reported case of histology-confirmed fenbendazole-induced severe DILI.

Our case also highlights the potentially severe consequences of the spread of medical misinformation through social media. Physicians should educate patients about such risks and inquire in detail about the self-administration of products other than formally listed medications.

DISCLOSURES

Author contributions: All authors made substantial contributions to the work were involved in the final approval of the version to be published and agree to be held accountable for all aspects of the work. MC Cave is the article guarantor.

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