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Single Case

Black Cohosh Hepatotoxicity with Autoimmune Hepatitis Presentation

Diana L. Franco^a Santosh Kale^b Dora M. Lam-Himlin^c
M. Edwyn Harrison^d

^aGastroenterology Fellow, Mayo Clinic, Scottsdale, AZ, USA; ^bBankura Sammilani Medical College, Bankura, India; ^cDepartment of Pathology and Laboratory Medicine, Mayo Clinic, Scottsdale, AZ, USA; ^dDivision of Gastroenterology and Hepatology, Mayo Clinic, Scottsdale, AZ, USA

Keywords

Black cohosh · Hepatotoxicity · Autoimmune hepatitis presentation

Abstract

Herbal medicines have been used for the treatment of various ailments since time immemorial. Black cohosh (BC) is well known for the treatment of postmenopausal symptoms, with conflicting evidence supporting its safety and benefits. We present a rare case of BC-induced autoimmune hepatitis (AIH) with hepatotoxicity in a 69-year-old female. To our knowledge, this represents the third case of BC-induced AIH.

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Introduction

Vasomotor symptoms are the cardinal symptoms of menopause, affecting more than three-quarters of midlife women. Nonprescription therapies include dietary isoflavones, vitamin E, and herbal remedies like black cohosh (BC) and Chinese herbs. BC (*Actaea racemosa* or *Cimicifuga racemosa*) is most widely used among the herbal preparations. Although

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Diana L. Franco, MD
Mayo Clinic
5777 E Mayo Blvd.
Phoenix, AZ 85054 (USA)
E-Mail franco.diana@mayo.edu

adverse events following the use of BC are infrequent, there are various literature reports of its adverse effects, ranging from liver failure to a weak correlation with hepatitis [1–4].

We present a rare case of BC-induced liver injury with autoimmune hepatitis (AIH) presentation following the 1-week use of over-the-counter BC for hot flashes. Based on the causality assessment algorithm of the Council for International Organizations of Medical Sciences (CIOMS), it fell into the highly probable category of drug-induced liver injury, whereas the liver biopsy with elevated serum markers confirmed its autoimmune nature. Other potential causes of liver injury such as biliary obstruction, viral hepatitis, hemochromatosis, or Wilson's disease were ruled out with appropriate tests.

Case Report

A 69-year-old female with a past medical history of hypertension and a remote history of hepatitis A infection presented to our institution with a 2-week history of sharp right upper quadrant pain and a 3-day history of dark urine and clay-colored stools. Her medications included amlodipine, metoprolol, and omeprazole, which she had been taking for years, and 150 mg of BC a day (root standardized extract) for her hot flashes, started 1 week prior to the onset of her symptoms. She denied any alcohol use, and her family history was negative for liver disease or autoimmune diseases.

Vital signs were within normal limits. Physical examination was significant for tenderness in the right upper quadrant and jaundice without any stigmata of chronic liver disease. On admission, liver function tests (LFTs) were elevated, with total bilirubin 6.3 mg/dL, direct bilirubin 4.9 mg/dL, alkaline phosphatase 296 IU/L, alanine transaminase 2,385 IU/L, and aspartate transaminase 1,386 IU/L; LFTs had been normal 1 year before. She had normal liver synthetic function with an international normalized ratio of 1 and albumin of 4.3 g/dL. Magnetic resonance imaging of the abdomen was unremarkable. Further evaluation was negative for acetaminophen level, urine drug screen, viral hepatitis panel, ceruloplasmin protein electrophoresis, and genetic testing for hemochromatosis. The autoimmune panel revealed elevated anti-nuclear antibody and anti-smooth muscle antibody (Table 1). Liver biopsy showed intense portal-based chronic inflammation with prominent plasma cell population and moderate lobular activity without necrosis or fibrosis, findings consistent with AIH (Fig. 1, Fig. 2).

BC was discontinued upon admission. Given the autoimmune pattern on biopsy, prednisone and azathioprine were started at a dose of 30 and 50 mg a day, respectively. Two days after the start of treatment and 5 days after the discontinuation of BC, LFTs started to decrease, with complete normalization after 3 months of treatment. Prednisone was discontinued after 3 months, followed by discontinuation of azathioprine after 6 months. The patient's LFTs remained normal after 1 year of follow-up without treatment.

Discussion

BC is a flowering plant native to Canada and the eastern United States. Its root has been used since time immemorial by the native Indian population for the treatment of postmeno-

pausal symptoms. Triterpene glycosides along with other phenolic constituents are believed to be the active ingredients [5]. Recent studies have shown conflicting evidence regarding its safety and efficacy [4, 6].

Extracts from BC are thought to possess an estrogen-like component potentially helping in vasomotor symptoms in menopausal women [7]. In 2014, Enbom et al. [8] demonstrated that the mechanism of hepatotoxicity through BC is due to the oxidative damage of the liver cells caused by the accumulation of protein adducts which serve as autoantigens and provoke an autoimmune response.

Causality assessment is a major clinical challenge, since temporal associations are not sufficient. Causality assessment may be achieved by a variety of algorithms. The CIOMS proposes a structured causality assessment algorithm that gives points to establish causality for drug-induced liver injury [9]. A score >6 makes the drug “probable” for inducing liver toxicity, and a score >8 makes the drug “highly probable” for causing hepatotoxicity. In our case, the causality assessment score was 10 points (Table 2).

There have been previous reports of BC hepatotoxicity; however, lack of basic information, such as on timing and comedication, interferes with causality assessment. In a review by Teschke et al. [4], 69 cases of reported BC toxicity were analyzed by causality algorithms. Only 1 case had “probable” BC-induced toxicity, with the remaining cases labeled as having confounding variables, such as use of herbal mixtures with multiple ingredients, missing temporal association between BC use and development of liver disease, and pre-existing liver diseases.

Drug-induced AIH (DIAIH) occurs due to immune response against the protein adducts formed within the liver, where they bind to cellular proteins and behave as autoantigens [10]. Drugs like minocycline and nitrofurantoin are some of the well-known causes of DIAIH, whereas BC-induced AIH has been reported in only 2 previous case reports [2, 11]. DIAIH is suspected in the presence of AIH with concurrent drug use, which was the case with our patient [12]. Liver biopsy along with serological markers helps to confirm the diagnosis. Interface hepatitis, usually associated with plasma cells, is an important finding. Autoantibodies are helpful, but not completely reliable, for the severity and the course [13, 14].

Our patient did not have the usual course for AIH, since she responded unusually rapidly to immunosuppressive therapy and has not relapsed after relatively early and complete withdrawal of therapy. To our knowledge, this is the first case of highly probable drug-induced injury as defined by formal scores and presenting with AIH.

In conclusion, hepatotoxicity causality assessment is a major clinical challenge, since temporal associations are not sufficient. The reported cases lack basic information, which interferes with causality assessment as it is not considered valid. Stricter FDA and governmental regulations need to be applied to the purity of herbal remedies like BC, as serious adverse effects like DIAIH can be seen.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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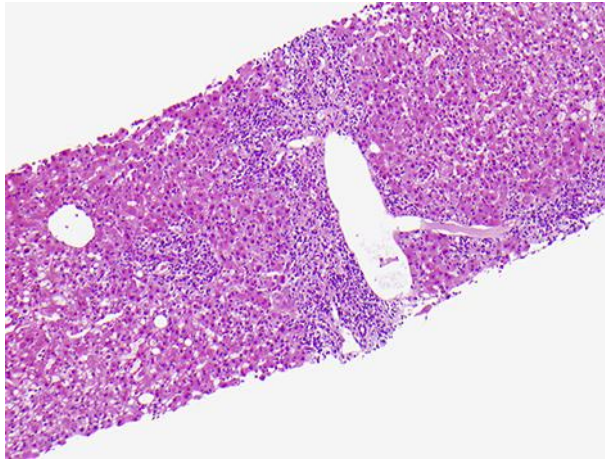


Fig. 1. Histologic sections show an prominent interface and lobular hepatitis. Hematoxylin and eosin. Original magnification, $\times 10$.

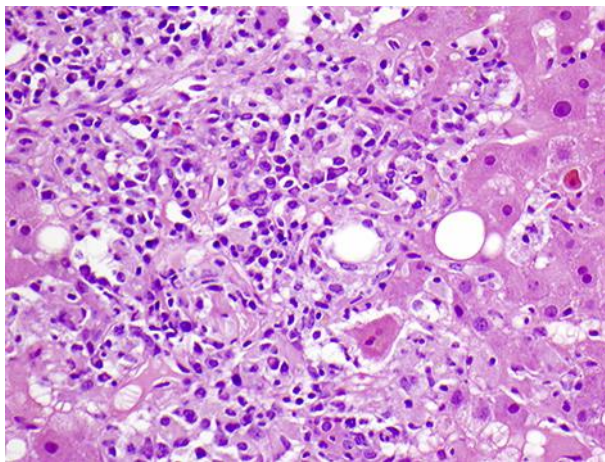


Fig. 2. Higher magnification highlights the plasma cell-rich infiltrate and single necrotic hepatocytes. A few eosinophils are also present, suggesting an element of drug-induced liver injury. Hematoxylin and eosin. Original magnification, $\times 40$.

Table 1. Laboratory values on the day of admission

Total bilirubin	6.3 mg/dL
Direct bilirubin	4.9 mg/dL
Anti-nuclear antibody	1.7
Anti-smooth muscle antibody	Pos 1:80
p-ANCA	Pos
Alkaline phosphatase	296 IU/L
Alanine transaminase	2,385 IU/L
Aspartate transaminase	1,386 IU/L

Table 2. Main test for hepatocellular injury

Main test criteria	Score
Time to onset from beginning of the drug	+2
Time to onset from cessation of the drug	+1
Course of ALT after cessation of the drug	+3
Risk factor – ethanol	0
Risk factor – age	+1
Concomitant drug(s)	0
Search for nondrug causes	+2
Previous information on hepatotoxicity of the drug	+1
Response to readministration	0
Total points	10

ALT, alanine transaminase.