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Case Report
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# A Case of Cholestatic Drug-Induced Liver Injury (DILI) Associated with Black Cohosh

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## Abstract

**Background:** Drug-induced Liver Injury is an uncommon yet fatal cause of liver injury. It is a major public health concern due to the rapid increase in the use of nonprescription drugs over the last decade. These drugs escape the testing by the Food and Drug Administration as these are considered as supplements. Black Cohosh is a herbal supplement that is derived from *Actaea racemosa*. It has been used for vasomotor symptoms in postmenopausal women but it has the potential to cause liver injury.

**Case Presentation:** A 50-year-old AAF presented with a 2-month history of malaise, itching, severe jaundice, and alopecia. The labs showed a significant elevation of bilirubin along with elevation of Alkaline phosphatase. The patient had a history of using Black Cohosh for two months for relief of postmenopausal hot flashes, two months after which she developed her current symptoms. The extensive workup for liver pathology including viral hepatitis, alcohol-related liver disease, metabolic, and autoimmune was negative. The patient was advised to discontinue using Black Cohosh. The patient improved clinically and her liver enzymes normalized six months after the discontinuation of Black Cohosh.

**Conclusion:** This report represents a case of cholestatic liver injury due to Black Cohosh therapy. It emphasizes the need to recognize Black Cohosh as a potential hepatotoxic agent and monitoring the LFTs for a patient on Black Cohosh.

**Keywords: Black cohosh; Cholestatic; Drug-induced liver injury**

## Introduction

Drug-Induced Liver Injury (DILI) is defined as liver injury caused by medications, herbal products, or other agents leading to abnormalities in liver biochemistries due to damage to liver parenchyma and the resultant liver dysfunction. Liver injury can be caused by almost all classes of drugs. The spectrum of liver injury ranges from being asymptomatic to a mild elevation of liver biochemistries to fulminant hepatic failure resulting in death or liver transplantation. Amongst the major areas of public health concern in the US, liver injury has been a front runner. DILI is the single most common cause of acute liver failure. The annual worldwide incidence of DILI has been reported at 0.014% to 0.024%. DILI has been the most reported cause of adverse drug reactions [1-3]. The exact measurement of the incidence of DILI has been a challenge. The factors posing this challenge involve DILI being a relatively uncommon entity along with under-reporting and under-recognition of this injury. Nearly half the cases of acute liver failure in the US alone are due to DILI. The case fatality rate has been about 10% to 50%. DILI can be either idiosyncratic or dose-dependent. Due to the rapidly expanding market of non-prescription drugs in the US, DILI has become an important etiology of acute liver injury. Non-prescription drugs do not undergo testing and escape the trials from the Food and Drug Administration as these are considered as supplements. However, due to rising concerns, the FDA has begun taking regulatory actions to implement guidelines involved with the use of these supplements [4,5]. The studies emphasize the timely and accurate reporting of DILI which is important for spreading awareness and early detection of DILI.

We present a case of Black Cohosh associated Cholestatic Liver Injury. Black Cohosh is a herbal product that is used for the treatment of vasomotor symptoms of menopause. The product is associated with common side effects including nausea, vomiting, weight gain, rash, and headache.

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## Case Presentation

A 50-year-old Afro-American woman was referred to our center for evaluation of worsening jaundice, malaise, itching, and significantly elevated liver enzymes. These symptoms started developing about two months before the presentation. The patient's medical history was significant for Asthma/COPD, type 2 diabetes mellitus, and iron deficiency anemia. There was no history of liver disease prior to these symptoms. Her medications included: Coreg 12.5 twice daily, Pepcid 20 daily, Symbicort, and Albuterol inhaler. She had a history of Black Cohosh use two months before the onset of the symptoms, for a total duration of two months. There was no history of substance abuse, no smoking history, and no history of alcohol use. She denied any history of blood transfusion, tattooing, or travel history. There was no history of any liver disease in the family.

The patient was feeling well and was in her usual state of health two months back when she started developing the symptoms of fatigue, nausea, and yellowing of the skin. She was seen at an outside hospital. Liver chemistries performed at the outside hospital revealed the following: Total bilirubin (TBIL) = 27.9 mg/dL, Alkaline Phosphatase (Alk Phos) = 201 U/L, Aspartate Aminotransferase (AST) = 24 U/L, Alanine Aminotransferase (ALT) = 33 U/L and Serum Creatinine = 1.04 mg/dL. Her INR was 1.06 and serum albumin was normal at 4.0 g/dL. Hemoglobin was 9.6 mg/dl; white blood cell count was 6.0/l, and platelet count of $468 \times 10^6$ cells/mL. Her immune workup at OSH was positive for AMA and she was started on Ursodiol. The patient had no relief in her symptoms. The patient's family noticed the worsening of the yellowing of her eyes and itching.

Due to the worsening of her clinical symptoms and significant hyperbilirubinemia, the patient was referred to our hospital. The patient presented with complaints of significant nausea, vomiting, poor appetite, 10-pound weight loss, and persistent jaundice. On presentation, the physical examination was significant for jaundiced skin and bilateral scleral icterus. The abdominal examination was unremarkable without tenderness, distension, or hepatosplenomegaly. The laboratory studies at presentation revealed the following: AST=26 U/L, ALT=37 U/L, TBIL=26.2 mg/dL, INR=1.02, Albumin = 3.6 g/dL and Alk Phos = 207 U/L. Drug levels for Alcohol and acetaminophen were undetectable. The workup for viral serology including Hepatitis A, Hepatitis B (HBV) sAg, HBc IgM, Hepatitis C (HCV) Ab, HIV Ag/Ab, Herpes Simplex (HSV) 1 and 2, Epstein Barr Virus (EBV), and Cytomegalovirus (CMV) was negative. The autoimmune workup was negative for antinuclear antibody, anti-smooth muscle antibody, anti-mitochondrial antibody, and anti-LKM antibody. The lab work was negative for Hemochromatosis and Wilson disease. Immunoglobulin and thyroid-stimulating hormone levels were within the normal range.

The CT scan of the abdomen was significant for the findings of multiple foci of hypoattenuation throughout the left and right hepatic lobes representing cysts or hemangiomas without any evidence for cirrhosis or biliary ductal dilation. Endoscopic Retrograde Cholangiopancreatography (ERCP) was performed and demonstrated that the common bile duct and common hepatic duct were approximately 5 mm, smooth, and without any stricture (Figure 1). The intra-hepatic and extra-hepatic biliary duct systems were completely normal with no missing secondary duct or ductal irregularities.

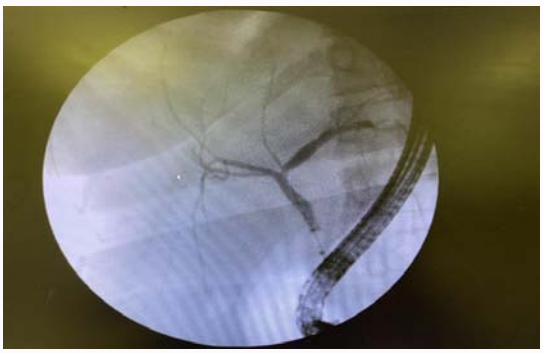

**Figure 1:** ERCP showing normal duct morphology.

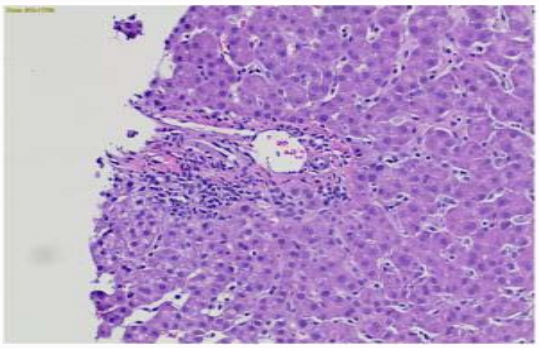

**Figure 2:** Mild portal and lobular inflammation.

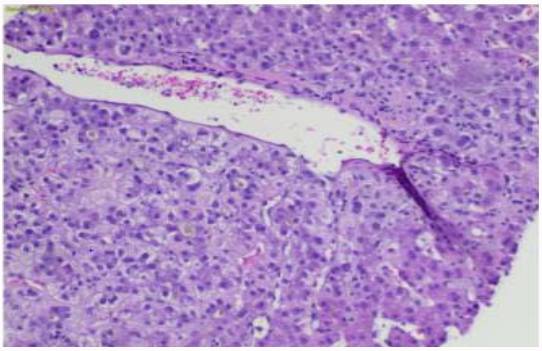

**Figure 3:** Bile canaliculi with stasis.

The percutaneous liver biopsy demonstrated mild lobular and portal inflammation, intrahepatic canalicular cholestasis, ductopenia of the interlobular bile ducts, and mild sinusoidal dilation (Figures 2-4) suggestive of more recent and significant hepatocyte injury, which correlated with the patient's clinical history. The patient was told to abstain from the use of Black Cohosh and was started on Budesonide for a short course concerning her worsening clinical picture.

After the drug withdrawal and treatment, the patient's enzymes started trending downwards. She started having an improvement in her clinical symptoms with the resolution of nausea, fatigue, and jaundice. Her liver enzymes showed normalization of her bilirubin and near normalization of her alkaline phosphatase over the next 6 months (Figure 5 and 6). The patient was counseled to avoid the use of Black Cohosh in the future. Re-challenge with the

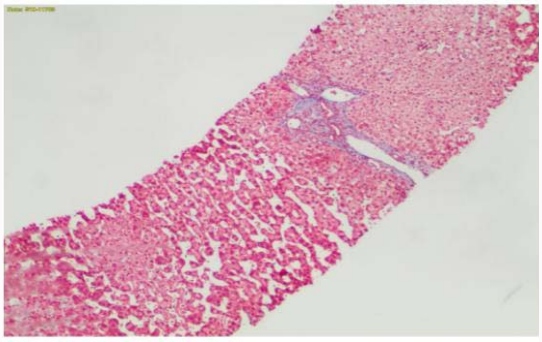

**Figure 4:** Trichrome stain showing acidophilic bodies, sinusoidal dilation, and fibrosis.

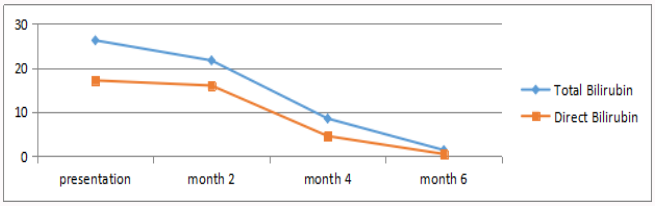


**Figure 5:** Graph demonstrating bilirubin trend.

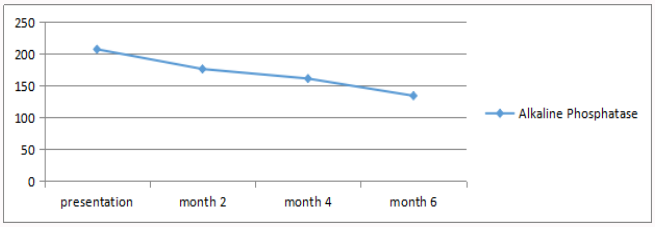


**Figure 6:** Graph showing alkaline phosphatase trend.

suspected agent was not attempted due to ethical reasons and for the safety of the patient.

## Discussion

Drug-induced liver injury is the single most common cause of acute liver failure. There have been increasing cases of DILI due to the rapid expansion of non-prescription medications in the last decade. Since the increase in the publication of data on the side effects of prescription medications, the use of over the counter medications is increasing due to presumed lesser side effect profile. The reported incidence of DILI has been between 0.01% to 0.001% from both prescription and non-prescription medications. DILI is under reported due to several factors, including the rarity of DILI, and the majority of cases being asymptomatic. The other factor contributing to this is the relatively small size of phase 2 and phases 3 clinical drug trials. The non-prescription products do not go through the testing from FDA as these are considered as supplements. There has been a database of hundreds of drugs that have been linked to DILI as the suspected agent. The severity of DILI ranges from being asymptomatic to vague symptoms of nausea, vomiting, and abdominal pain to severe hepatic injury leading to fulminant hepatic failure requiring liver transplantation and to death. DILI can be divided into predictable or dose-dependent and dose-independent idiosyncratic [6-8]. There have been extensive data on the dose-dependent liver damage as explained by the Acetaminophen-induced liver toxicity. The idiosyncratic drug-induced liver injury represents a complex interaction involving the drug morphology and the human genetic framework and the unique metabolism characteristics of each person [9,10]. The idiosyncratic drug-induced injuries have been reported mostly in the case reports. There has been an increase in the reporting of data about these idiosyncratic drug injuries due to the publication of data encompassing the relatively known drugs. Therefore, these drug injuries may not be recognized until phase 4 of the drug trial, when the drug is launched in the market with thousands of patients being exposed to it and hence leading DILI to be recognized.

The diagnosis of DILI is challenging. It is usually a diagnosis of exclusion. There are no specific tests that are proven for the diagnosis of DILI. DILI is usually diagnosed when all the other causes have been ruled out as it is essentially a diagnosis of exclusion. There are a multitude of factors that further make the diagnosis challenging including a preexisting liver pathology or the patient being on multiple potential hepatotoxic agents. The evaluation includes an extensive workup including laboratory tests and clinical assessment encompassing all pathology which includes: Autoimmune liver diseases, viral hepatitis, metabolic disorders, alcohol use disorders, vascular disorders of the liver, hepatic ischemia, and biliary tract disorders.

The most likely etiology in our case report was Black Cohosh induced DILI. The extensive workup starting from the history and clinical examination to lab work and imaging was insignificant. The patient did not have any history of prior liver disease. The workup for autoimmune markers and viral serology was negative. The imaging was not suggestive of any hepatic ischemia or biliary tract obstruction.

DILI has been classified taking into account the different factors. One of the most commonly used markers is the R factor. The R factor was introduced in 1989 at an international consensus meeting. The R factor is calculated by taking into consideration the patient's lab values of Alanine Transaminase and Alkaline Phosphatase and comparing it to the normal values. There are three main classifications of DILI:

1. Hepatocellular Damage;
2. Cholestatic Damage; and
3. Mixed Liver Damage [11].

Hepatocellular injury is characterized by significant damage to the hepatocytes with the R factor being >5 and AST, ALT being more elevated as compared to the ALP levels. Cholestatic injury is due to direct injury to the biliary tract with the R factor being <2 and ALP, Bilirubin being significantly elevated. Mixed injury is a combination of both the hepatocellular and cholestatic pattern. In this case, the R factor is 2 to 5. A disproportionately elevated T. Bilirubin is characteristic of a more severe liver injury. In the case presented above, our patient had a cholestatic injury with a disproportionately elevated T. Bilirubin and mildly elevated ALP, consistent with a moderately severe liver injury.

The biggest challenge in DILI is to establish a relationship with the causative agent. There have been different scales that are used for the assessment of the causative agent in DILI. These are the Roussel Uclaf Causality Assessment Model [RUCAM] Scale and

Maria & Victorino (M&V) Scale. These are however not the perfect scales to guide the assessment of a patient with a suspicion of DILI [12,13]. The RUCAM Scale includes several variables that include: Chronological criteria (time from drug intake until onset and time from drug withdrawal until onset), course of the reaction, risk factors, concomitant therapy, exclusion of other causes, previously published data, and the response of re-challenge to the suspected agent. Depending upon the grading on the scale, a score between -9 to +14 is obtained. The offending agent is classified as; excluded, unlikely, possible, probable, and highly probable. On the RUCAM scale, our patient had Black Cohosh as the 'probable' cause of DILI. The M&V is the simplified version of the RUCAM scale. The M&V scale has different variables including the chronological criteria (from drug intake until onset and from drug withdrawal until onset), course of the reaction, and exclusion of other causes, extra-hepatic manifestations, known reactions, and re-challenge with the same agent. Depending upon the grading on the scale, a score of −8 to 20 is obtained. The offending agent is then categorized as; unlikely, possible, probable, and definite. Using the M&V scale, our patient had Black Cohosh as a "possible" cause of DILI. The major drawback to the RUCAM and the M&V scale is the great emphasis laid upon the re-challenge with an offending agent resulting in DILI. The re-challenge with Black Cohosh was not attempted due to ethical reasons and for concerns for patient safety. Black Cohosh is derived from the extracts of the plant *Actaea racemosa*. It is a herbal supplement that was used in historical times for the treatment of arthralgias and myalgias. After the publication in the Women's Health Initiative about increased cardiovascular risks due to hormone replacement therapy, more and more women are trying alternative therapies including Black Cohosh for the treatment of postmenopausal vasomotor symptoms.

Black Cohosh has been cited in multiple case reports. The published data has reported cases ranging from mild self-limited injury to fulminant hepatic failure. The spectrum ranges from mild hepatitis, autoimmune hepatitis, hepatitis with cholestasis, and hepatic failure requiring transplant [14]. The mechanism of action of Black Cohosh causing liver injury is unknown but it is suspected to be due to oxidative damage from the accumulation of byproducts in cells and the migration of inflammatory mediators [15]. The time duration between the first dose and the onset of symptoms has ranged from 1 to 48 weeks but usually, it has been within the 2 to 12 weeks [16].

There has been controversy regarding the relationship between Black Cohosh and liver injury. There have been multiple reports of Black Cohosh induced liver injury but there have been multiple discrepancies. There has been limited data on the dosing, purity of the product, source and preparation of the compound, and the temporal relation. Most of the Black Cohosh products available over the counter have multiple ingredients and unknown compounds. The review of the articles on Black Cohosh was done by Teschke et al. [17]. It was found that most of the cases had confounding variables including pre-existing liver pathology, herbal products with multiple ingredients, and the lack of chronological relation. Only one case was found to be truly of Black Cohosh induced hepatotoxicity. Therefore, the conclusion was reached that there has not been enough data to suggest a causal relationship [17].

Black Cohosh was the most likely cause of cholestasis type DILI in our patient. There was no change in her medications. She denied the use of any other herbal products or any other over the counter supplements. She had been on Coreg and Albuterol for years and had no issues before developing these symptoms. The patient improved on stopping Black Cohosh while being on the other medications at the same time. The extensive workup was inconclusive, hence leading to Black Cohosh being the offending agent. The exact compound leading to DILI in Black Cohosh could not be found as its ingredients include isoflavones, magnolia bark extracts, and tea leaf extracts.

This case emphasizes the increasing number of side effects of herbal products, highlights the need for strict regulation on their use and stresses the importance of awareness among people using these products. These herbal products are thought to be natural and hence free from side effects. Awareness should be created among the consumers regarding the potential risk factors. There is an urgent need to spread knowledge among health-care workers regarding reporting and early diagnosis of these events. The health care providers also need to be aware of the fact that there could be a long latency period before the signs show up and thus an extensive workup including medical history and the current and past herbal supplements should be obtained when evaluating a patient with liver injury.

## References


1. Aithal GP, Rawlins MD, Day CP. Accuracy of hepatic adverse drug reaction reporting in one English health region. BMJ. 1999;319(7224):1541.
2. Friis H, Andreasen PB. Drug-induced hepatic injury: An analysis of 1100 case reports to the Danish Committee on Adverse Drug Reactions between 1978 and 1987. J Intern Med. 1992;232(2):133-8.
3. Dossing M, Andreasen PB. Drug-induced liver disease in Denmark. An analysis of 572 cases of hepatotoxicity reported to the Danish Board of Adverse Reactions to Drugs. Scsnd J gastroenterol. 1982;17(2):205-11.
4. Bell LN, Chalasani N. Epidemiology of idiosyncratic drug-induced liver injury. Semin Liver Dis. 2009;29(4):337-47.
5. Watkins PB, Seeff LB. Drug-induced liver injury: Summary of a single topic clinical research conference. Hepatology. 2006;43(3):618-31.
6. Navarro VJ, Senior JR. Drug-related hepatotoxicity. N Engl J Med. 2006;354(7):731-9.
7. Larson AM, Polson J, Fontana RJ, Davern TJ, Lalani E, Hynan LS, et al. Acetaminophen-induced acute liver failure: Results of a United States multicenter, prospective study. Hepatology. 2005;42(6):1364-72.
8. Abboud G, Kaplowitz N. Drug-induced liver injury. Drug Saf. 2007;30(4):277-94.
9. Fontana RJ. Acute liver failure due to drugs. Semin Liver Dis. 2008;28(2):175-87.
10. Graham DJ, Green L, Senior JR, Nourjah P. Troglitazone-induced liver failure: A case study. Am J Med. 2003;114(4):299-306.
11. Hayashi PH. Causality assessment in drug-induced liver injury. Semin Liver Dis. 2009;29(4):348-56.
12. Garcia-Cortes M, Stephens C, Lucena MI, Fernandez-Castaner A, Andrade RJ. Causality assessment methods in drug induced liver injury: Strengths and weaknesses. J Hepatol. 2011;55(3):683-91.
13. Centers for Disease Control and Prevention.
14. Lim TY, Considine A, Qualgia A, Shawcross DL. Subacute liver failure secondary to black cohosh leading to liver transplantation. BMJ Case Rep. 2013;2013:bcr2013009325.

15. Enbom ET, Le MD, Oesterich L, Rutgers J, French SW. Mechanism of hepatotoxicity due to black cohosh (*Cimiciguga racemose*): Histological, immunohistochemical and electron microscopy analysis of twoliver biopsies with clinical correlation. Exp Mol Patholol. 2014;96(3):279-83.

16. U.S. National Library of Medicine. Black Cohosh (Actaea Racemosa). LiverTox. Clinical and research information on drug-induced liver injury. 2018.

17. Teschke R, Bahre R, Genthner A, Fuchs J, Schmidt-Taenzer W, Wolff A. Suspected black cohosh hepatotoxicity – challengesand pitfalls of causality assessment. Maturitas. 2009;63(4):302-14.