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Case Report

A Case of Sub Acute Liver Failure Associated with Black Cohosh Use

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Abstract

Black cohosh is an herbal medication used for the treatment of postmenopausal vasomotor symptoms. We report a case of sub acute liver failure associated with black cohosh use. A 50 year-old female with hypertension, uterine fibroids, and recent hospitalization for acute hepatitis secondary to black cohosh was readmitted with asterixis and confusion. Two months prior, she started black cohosh and developed scleral icterus, abdominal pain, nausea, and vomiting. She had no underlying liver disease. Medications included hydrochlorothiazide and metoprolol. Family history was significant for autoimmune hepatitis. She had a 4 pack-year smoking history and endorsed having one drink daily for 10 years, but quit two months ago. Physical exam on initial presentation was remarkable for jaundice. Her liver function tests (LFTs) were abnormal, but no coagulopathy. Hepatitis panel and autoimmune serologies were normal. RUQ ultrasound suggested hepatic steatosis. Liver biopsy revealed severe acute hepatitis with sub massive hepatic necrosis. The patient was discharged with improved LFTs on prednisone. One month later, the patient presented with asterixis and confusion. Lab studies revealed abnormal LFTs, elevated serum ammonia, and coagulopathy. A diagnosis of sub acute liver failure was made. The patient did not require a transplant and recovered with conservative management. The patient scored 5 on the Roussel UCLAF causality assessment method, suggesting black cohosh as a probable cause of her liver injury. In conclusion, we present a case of black cohosh associated sub acute liver failure which developed weeks after the initial insult. This case underscores the importance of close follow-up after the initial insult.

ABBREVIATIONS

ALP: Alkaline Phosphatase; ALT: Alanine Aminotransferase; AMA: Anti-Mitochondrial Antibodies; ANA: Anti-Nuclear Antibodies; AST: Aspartate Aminotransferase; C-ANCA: Cytoplasmic Anti-Neutrophil Cytoplasmic Antibodies; CBC: Complete Blood Count; CMP: Comprehensive Metabolic Panel; CMV: Cytomegalovirus; CT: Computed Tomography; EBV: Epstein-Barr Virus; GGT: Gamma-Glutamyltranspeptidase; HAV: Hepatitis A Virus; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HEV: Hepatitis E Virus; HIV: Human Immunodeficiency Virus; HSV: Herpes Simplex Virus; Igg: Immunoglobulin G; Igm: Immunoglobulin M; INR: International Normalized Ratio; P-ANCA: Perinuclear Anti-Neutrophil Cytoplasmic Antibodies; PCR: Polymerase Chain Reaction; PT: Prothrombin Time; PTT: Partial Thromboplastin Time; RUQ: Right Upper Quadrant; VZV: Varicella Zoster Virus

INTRODUCTION

Black cohosh, also known as *Actaearacemosa* or *Cimicifugaracemosa*, is one of the most frequently used herbal medications to treat postmenopausal vasomotor symptoms [1]. Although black cohosh is generally considered relatively safe [2], it has been associated with hepatotoxicity. In 2007, the European Medicine Agency (EMEA) extensively reviewed a number of black cohosh-induced liver injury cases and concluded that one should discontinue black cohosh if signs and symptoms of liver injury develop [3]. However, a recent meta-analysis of five randomized controlled clinical trials suggested that black cohosh had no adverse effects on liver function [4]. As of this writing, the possibility of liver injury with black cohosh use remains a matter of concern. Herein, we report a case of subacute liver failure associated with black cohosh use.

CASE PRESENTATION

Our patient is a 50 years-old African American female with past medical history significant for hypertension, uterine fibroids, and a recent hospitalization at an outside hospital with acute hepatitis secondary to black cohosh use. Two months prior to her presentation to our institution, she started a daily course of an over-the-counter black cohosh preparation to treat hot flashes. Menstrual history suggested perimenopausal status in our patient. It was not ascertained which commercial preparation of black cohosh and what does she had taken. Two weeks after black cohosh use, she was admitted to an outside hospital for yellowing of eyes, abdominal pain, nausea, and vomiting. She had no documented underlying liver or autoimmune disease. Her surgical history was unremarkable. Her medications included hydrochlorothiazide 25 mg p.o. daily and metoprolol 25 mg p.o. daily. She had no known drug or food allergies. Her family history was significant for autoimmune hepatitis, hypertension, and coronary artery disease. She had a 4 pack-year smoking history and endorsed having one alcoholic drink daily for 10 years, but quit two months ago. She denied current and past illicit drug use. She denied any history of blood transfusions or tattoos. Physical examination was remarkable for scleral and sublingual icterus only. Her liver enzymes (AST: 3,007 IU/mL, ALT: 2,072 IU/mL) and bilirubin (total bilirubin: 16.9 mg/dL, direct bilirubin: 10.3 mg/dL) were markedly elevated. Her ALP and GGT were 155 IU/mL and 203 µU/mL, respectively. Her PT, PTT, and INR were 17.7 s, 37.7 s, and 1.45, respectively. Serum ammonia was elevated at 54 µmol/L. Her CMP showed hypoalbuminemia at 2.7 gm/dL. The IgG level was 1,811 mg/dL. Serologic tests for HAV, HBV, HCV, HEV, ANA, p-ANCA, c-ANCA, anti-myeloperoxidase antibody, anti-proteinase-3 antibody, and anti-mitochondrial antibody (AMA) were all negative. Serum levels of ceruloplasmin, alpha-1-antitrypsin, and acetaminophen were within normal limits. Her CBC with differential, HbA1c, lipid panel, lipase, amylase, cardiac enzymes, urinalysis, urine culture, and urine toxicology were all unremarkable as well. Chest x-ray and CT scan of abdomen and pelvis without contrast were both within normal limits. Right upper quadrant ultrasound suggested possible mild hepatic steatosis. Percutaneous liver biopsy revealed severe acute hepatitis with submassive hepatic necrosis (Figure 1). The patient was discharged on day 9 of hospitalization on prednisone 40 mg p.o. daily. On the day of discharge, her ALT and AST markedly improved to 1,003 IU/mL and 1,279 IU/mL.

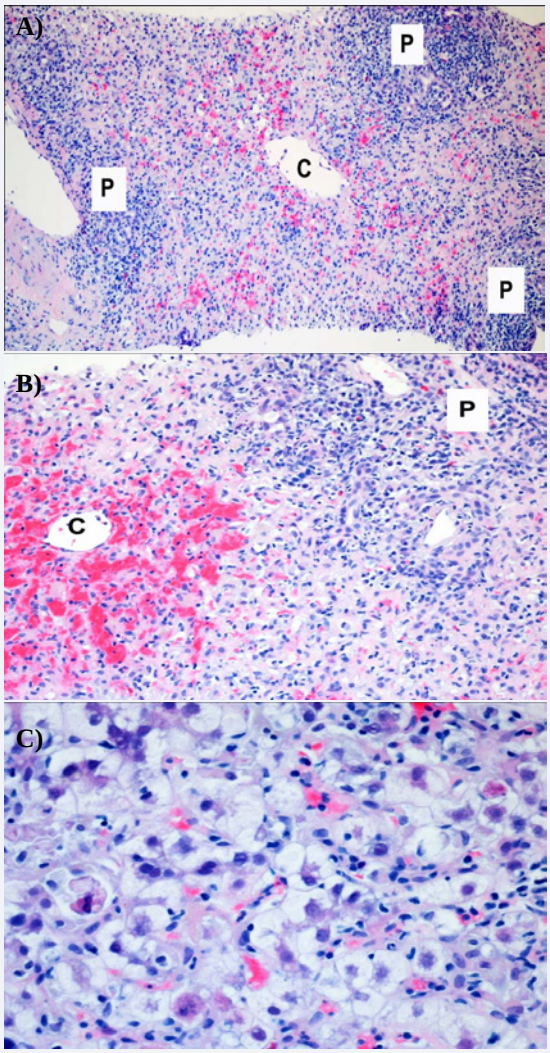

Figure 1 A) Low power photograph showing an area of complete loss of hepatocytes and stromal collapse. Inflamed portal tracts (P) and central veins (C) remain. B) Medium power photograph of a collapsed area showing inflammatory cells and hemorrhage between portal tracts (P) and central vein (C) but no remaining hepatocytes. C) High magnification of an area with residual parenchyma. There is a lymphocytic infiltrate, and the hepatocytes are ballooned and dying by apoptosis (Photomicrograph courtesy of Dr. Zachary Goodman, Inova Fairfax Hospital).

One month after discharge, the patient presented to our hospital with a 1-day history of asterixis and mild confusion. Medications at the time of admission included prednisone 40 mg p.o. daily, hydrochlorothiazide 25 mg p.o. daily, and metoprolol 25 mg p.o. daily. The patient was no longer taking black cohosh. Prednisone was held at the time of admission. Physical examination was notable for slowed mentation, slurred speech, asterixis, profound scleral and sublingual icterus, mild right upper quadrant tenderness, and mild pitting edema in the lower extremities. Laboratory studies revealed abnormal liver function tests (AST: 644 IU/mL, ALT: 501 IU/mL, total bilirubin: 26.54 mg/dL, direct bilirubin: 17.88 mg/dL, ALP: 496 IU/mL, PT: 21.5 s, INR: 2.01), elevated serum ammonia of 159 µmol/L, and positive anti-smooth muscle antibody of 88 IU/mL. Her CMP, CBC with differential, calcium, magnesium, and phosphate were all within normal limits. CMV IgM was negative. EBV DNA PCR was positive. VZV IgM and IgG were both elevated at 1.11 IU/mL and 2.31 IU/mL, respectively. Serological tests for HBV, HCV, HIV, HSV-1/2, ANA, AMA (2.5 U/mL), and anti-liver kidney microsomal antibodies (2.6 IU/mL) were all negative. Serum levels of alpha-1-antitrypsin, ceruloplasmin, acetaminophen, and salicylate were within normal limits. Urinalysis, thyroid studies, iron studies, and rapid plasmin reagin were unremarkable as well.

The presence of mixed hepatocellular/cholestatic liver injury, coagulopathy, and hepatic encephalopathy in our patient rendered a clinical diagnosis of subacute liver failure. On the second day of hospitalization, the patient was evaluated for liver transplantation, but subsequently transported to a transplant

center in her state of residency. The patient recovered with conservative management and did not require a transplant.

DISCUSSION

We described a case of sub acute liver failure secondary to black cohosh use in a perimenopausal woman.

In 2007, the European Medicine Agency (EMEA) reviewed 44 black cohosh-induced liver injury cases [3]. The agency examined the causal relationship between black cohosh and hepatotoxicity in each case based on the Roussel UCLAF causality assessment method (RUCAM). The RUCAM gives an overall assessment score on the likelihood that liver injury is a result of a specific medication based on the clinical, biochemical, serologic, and radiologic features of the liver injury [5]. Among the cases evaluated by the EMEA, only 5 cases could be classified as possible (RUCAM score: 3-5) or probable (RUCAM score: 6-8). In two of these cases, black cohosh was determined as a possible cause of liver failure [6, 7]. Two more reports of black cohosh-induced liver failure were published in literature since the completion of the EMEA study [8, 9], but their RUCAM scores are unknown. Our patient scored 5, suggesting that black cohosh has possibly caused her liver failure.

In conclusion, patients and healthcare professionals should be aware that the use of black cohosh can result in liver failure. Particularly, it should be noted that subfulminant liver failure can develop weeks after the initial insult and therefore close follow-up monitoring is required. Our patient developed new onset encephalopathy and coagulopathy one month after initial presentation, despite improving transaminitis. Patients with any underlying liver disease or history of alcoholism should further reconsider its use and consult healthcare professionals before initiating the herbal treatment. This case underscores the urgent need for federal regulations to be instituted to oversee the manufacturing, marketing, and safety of herbal preparations.

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