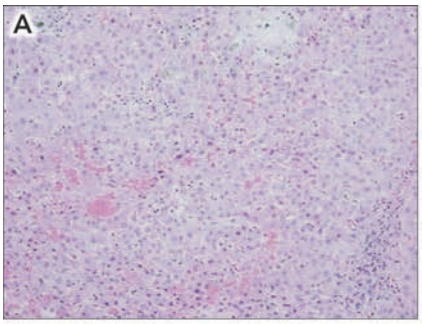
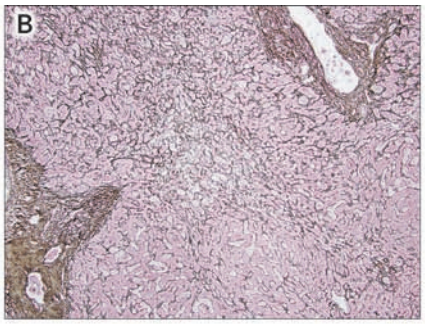
Liver failure associated with the use of black cohosh for menopausal symptoms

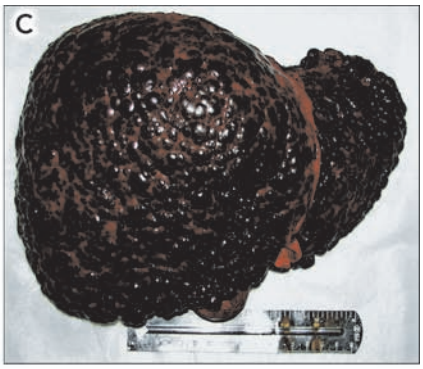
Elizabeth C-Y Chow, Marcus Teo, John A Ring and John W Chen



A: *Liver biopsy specimen, showing hepatocellular necrosis with preserved bile ducts and a marked mononuclear infiltrate (haematoxylin and eosin stain; high power).*



B: *Liver biopsy specimen, showing collapse due to hepatocyte necrosis (reticulin stain; high power).*



C: *Explanted liver, showing nodules.*

Clinical record

A 51-year-old woman of European ancestry presented in 2006 with a 2-month history of lethargy, nausea and arthralgia, and 2 weeks of jaundice. Her past history included gastric bypass surgery for obesity at the age of 40 years, and laminectomy. She had been taking a commercial preparation of black cohosh (20 mg per day) intermittently for 3 years, with titration according to her menopausal symptoms. This preparation was available over the counter. It contained 20 mg of black cohosh root extract per tablet, and the manufacturer recommended a dose of 20 mg twice daily. Two months before symptom onset, the patient increased the dose to the manufacturer's recommended dose because of worsening menopausal symptoms.

The patient was not taking any other medications, including other herbal preparations, paracetamol, or non-steroidal anti-inflammatory drugs. She had no personal or family history of liver disease. She was an ex-smoker, with no history of illicit drug use, significant alcohol consumption, recent travel, tattoos, transfusions or sick contacts. Physical examination revealed jaundice and mild ascites, but no evidence of hepatic encephalopathy or stigmata of chronic liver disease.

Results of laboratory studies were consistent with acute hepatitis. Serum albumin concentration was 36 g/L (reference range [RR], 31–44 g/L); elevations were noted in serum concentrations of aspartate aminotransferase (AST) (1327 U/L; RR, < 40 U/L), alanine aminotransferase (ALT) (1230 U/L; RR, < 50 U/L), alkaline phosphatase (ALP) (191 U/L; RR, 30–110 U/L), γ-glutamyltransferase (GGT) (523 U/L; RR, < 40 U/L), and bilirubin (106 μmol/L; RR, < 20 μmol/L). The international normalised ratio (INR) was 1.8 (RR, 1.0–1.2), serum creatinine concentration was 58 μmol/L (RR, 45–90 μmol/L) and MELD (Model for End-Stage Liver Disease) score was 16 (a score > 15 indicates that prognosis at 1 year will be improved by transplantation).

Extensive investigations to exclude other causes of acute liver failure gave negative results, including serological tests for hepatitis A, B, and C; cytomegalovirus IgM; Epstein–Barr virus IgG and IgM; antinuclear antibody; anti-liver/kidney microsomal antibodies; antimitochondrial antibody; anti-smooth muscle antibody, α-1 antitrypsin; ceruloplasmin; and fasting iron studies.

Abdominal computed tomography 1 month after presentation showed moderate ascites and a shrunken irregular liver contour, with a liver volume of 720 mL. Prominent vessels around the lesser curvature of the stomach suggested portal hypertension with collateral vessel formation. Doppler ultrasound examination a month later confirmed a small liver with coarse heterogeneous echotexture, and a macronodular surface. The portal vein was patent.

A liver biopsy 6 weeks after presentation showed massive hepatocellular necrosis with preserved bile ducts, collapsed parenchyma, and no recognisable residual hepatocytes (Figures, A and B). There were extensive mononuclear inflammatory infiltrates with few neutrophils. Perls staining was negative for iron.

A diagnosis was made of acute liver injury secondary to black cohosh ingestion. Over the subsequent weeks, the patient's jaundice worsened, and her serum bilirubin level continued to rise. Frusemide was given to manage developing moderate ascites.

Sixty-two days after presentation, the patient developed asterixis ("hepatic flap"), indicating encephalopathy and liver failure. She was diagnosed with subfulminant liver failure suitable for liver transplantation and was listed urgently for transplant. Liver function tests showed a serum albumin concentration of 30 g/L and elevated serum concentrations of AST (202 U/L), ALT (73 U/L), ALP (191 U/L), GGT (64 U/L) and bilirubin (728 μmol/L). The INR was 1.8. Her renal function rapidly deteriorated, with serum creatinine concentration rising to 255 μmol/L. The MELD score reached 37.

A liver became available 5 days after the patient was listed, and a successful orthotopic liver transplantation was performed. Her postoperative course was uneventful.

The explanted liver weighed 744 g and was distorted by multiple nodules of varying size, from 5 mm to 50 mm (Figure, C). Microscopically, there were areas of extensive submassive necrosis, capsule distortion, collapse of the hepatic parenchyma, and mononuclear inflammatory infiltrates around the portal tracts. Cholestasis was prominent. Nodular regeneration with portal–portal linkage was also evident in some areas, as seen in the pretransplant biopsy. ◆

Lessons from practice

- Black cohosh is a herbal remedy used by millions of women worldwide for the relief of menopausal symptoms.
- Emerging evidence of severe hepatotoxicity potentially linked with the use of black cohosh has raised concerns regarding its safety profile.
- The community needs to be educated about potential risks of alternative and herbal medications such as black cohosh, and further regulations are required to monitor the safety of these preparations. ◆

Black cohosh is a herbal remedy used around the world for relief of menopausal symptoms. In Australia, over 200 listed medicines containing black cohosh are available without prescription.[1] However, in the past decade, seven case reports of hepatotoxicity associated with black cohosh have been published.[1-7] To our knowledge, our patient is the eighth reported case, and the sixth to require liver transplantation.

Black cohosh (*Cimicifuga racemosa*, also known as *Actaea racemosa*) is a perennial plant native to North America. The World Health Organization recognises its use for "treatment of climacteric symptoms such as hot flushes, profuse sweating, sleeping disorders and nervous irritability".[8] The American College of Obstetricians and Gynecologists stated that it may be helpful in the short term (6 months or less) for women with vasomotor symptoms of menopause.[9] Although the exact mechanism of action is unknown, the primary active constituent of the black cohosh root is the terpene glycoside fraction, and the rhizome contains biologically active substances, including alkaloids, flavonoids, and tannins. However, despite the growing literature on the efficacy of black cohosh for menopausal symptoms, definite conclusions cannot be drawn because of the methodological shortcomings of available studies, such as lack of blinding, lack of long-term follow-up, and variations in product and dosage.[10-12]

Two safety reviews have found black cohosh extract to be well tolerated and adverse events to be rare when it is taken for up to 6 months.[13,14] However, the seven case reports of hepatotoxicity potentially associated with black cohosh use in the past decade raise concern. Currently, there is no known biologically plausible mechanism to explain this hepatotoxicity, which is likely to be multifactorial. The plant contains both potentially hepatoprotective (triterpene glycosides) and hepatotoxic (salicylates, alkaloids) elements. Extracts and constituents of the rhizome have been shown to induce apoptosis and cell cycle arrest in human breast cancer cells,[15,16] while extracts of the related plants *Cimicifuga foetida* and *Cimicifuga dahurica* inhibited proliferation of rat and mouse hepatocytes.[17]

The most likely cause of our patient's liver failure was her use of black cohosh, although it has been recognised that 10% of patients receiving liver transplantation have idiopathic subfulminant liver failure.[18] Our patient's history of obesity treated with gastric bypass surgery 11 years before is unlikely to have contributed to the liver failure as she had shown no abnormalities of liver function previously, and no features of steatohepatitis were seen in the pretransplant liver biopsy specimens. Our case is also notable as the patient had used black cohosh intermittently at half the manufacturer's recommended dose for 3 years, and at the manufacturer's recommended dose (20 mg twice a day) for only 2 months before symptom onset.

There is a widespread belief in the community that "natural" plant substances are safe, effective and free of side effects. Various regulatory bodies now recognise the association between black cohosh use and hepatotoxicity, and many recommend warning labels. The Therapeutic Goods Administration (TGA) was the first in the world to announce, in February 2006, that medicines containing black cohosh must include the label: "Warning: black cohosh may harm the liver in some individuals. Use under the supervision of a healthcare professional".[19] In November 2007, the TGA revised the warning to: "In very rare cases, black cohosh has been associated with liver failure. If you experience yellowing of the skin or eyes, dark urine, nausea, vomiting, unusual tiredness, weakness, stomach or abdominal pain, and/or loss of appetite, stop using this product and see your doctor".[20]

Randomised controlled trials will provide more definitive information on the safety of black cohosh and its efficacy for alleviating menopausal symptoms. Animal models may provide useful information about the cause of idiosyncratic liver damage. The public needs to be educated about the potential risks of alternative and herbal medications, and further regulations are required to monitor the use and safety of these preparations. Currently, there are no agreed guidelines for monitoring liver function in patients taking black cohosh. We recommend that liver function be checked before and during use of black cohosh.

Competing interests

None identified.

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(Received 2 Oct 2007, accepted 23 Jan 2008) ❑