A Serendipitous Find: A Case of Cholangiocarcinoma Identified Incidentally After Acute Liver Injury Due to *Cascara sagrada* Ingestion

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Abstract

The use of anthranoid laxatives such as Cascara sagrada *can, in rare instances, produce a hepatitis that resolves with discontinuation of the offending supplement. However, the clinical presentation of abdominal pain, jaundice, clay-colored stools, and darkening urine can mimic the presentation of a variety of hepatobiliary illnesses, including cholangiocarcinoma. This case report describes a local patient diagnosed with an extrahepatic cholangiocarcinoma following workup for an acute hepatitis due to ingestion of large quantities of* Cascara sagrada.

Keywords

Drug-induced liver injury, cholestasis, cholangiocarcinoma, cascara, jaundice

Introduction

Anthranoid laxatives, such as senna and *Cascara sagrada*, are commonly used for the treatment of constipation because of their botanical origin.[1] However, over the past 15 years, several cases of liver injury related to the use of these laxative agents have been reported. In the majority of these cases, the affected patient presented with symptoms of an acute hepatitis, including abdominal pain, jaundice, clay-colored stools, darkening urine, and elevated transaminase levels following chronic use or acute ingestions of large quantities of these supplements.[2-8]

The diagnosis of acute liver injury due to an herbal supplement is one of exclusion. In addition to basic laboratory studies such as a metabolic panel, viral serologies, liver function tests, and urine toxicology screens, abdominal imaging, typically ultrasonography is also warranted.[9] In an elderly patient, a high suspicion for malignancy should be maintained. In this report, we describe and discuss a patient who presented with acute liver injury following the ingestion of large quantities of *Cascara sagrada* over a 3-day period for the treatment of constipation, who, during the course of the workup for acute liver injury, was diagnosed with an extrahepatic cholangiocarcinoma.

Case Report

This is a 77-year-old Japanese woman, with a past medical history of hypertension, hyperlipidemia, and diabetes mellitus type II, treated with once daily dosing of verapamil ER 240 mg, losartan-hydrochlorothiazide 100-12.5 mg, lovastatin 50 mg, and metformin ER 500 mg. She presented to her primary care physician with a 10-day history of dark-colored urine, clay-colored stool, fatigue, and generalized jaundice. Immediately prior to the onset of these symptoms, the patient had experienced a 2-3 day period of constipation, for which she used an over-the-counter *Cascara sagrada*-based supplement, taking 3 capsules on the first day of constipation, and then 4 capsules on the two subsequent days, with relief of her constipation on the third day. Each capsule contained 250 mg of *Cascara sagrada* bark, along with small amounts of twelve other herbal supplements, and the recommended regimen was 1 to 3 capsules per day in divided doses. The patient had never used this supplement in the past.

Following the relief of her constipation, the patient stopped the use of this supplement. However, with the return of normal bowel function, the patient noted pale, clay-colored stools and clear, dark, orange-colored urine. Her stool color returned to normal within a week, but her urine remained discolored at the time of presentation. The patient finally presented to her primary care physician on the tenth day after the return of normal bowel function, when she noted 2 days of increased fatigue and a yellowish-tinge to her skin and eyes. The patient denied any urinary symptoms, including dysuria, burning, frequency, hesitancy, or flank pain, as well as any change in appetite, fever, chills, nausea, vomiting, constipation, diarrhea, hematochezia, or abdominal pain. Her physical examination revealed generalized jaundice without appreciable hepatomegaly or stigmata of liver disease. The remainder of her physical examination was within normal limits.

The patient was subsequently admitted for observation with a working initial diagnosis of acute liver injury due to the ingestion of an herbal supplement, to rule out more serious medical conditions. Initial laboratory workup included a complete metabolic panel, CBC with differential, urinalysis, hepatic profile, acetaminophen levels, hepatitis A, B, and C serologies, coagulation studies, and urine toxicology screen. The patient's metabolic panel and CBC were within normal limits. Consistent with acute liver injury, urinalysis showed clear (normal appearance: clear), orange-yellow (normal color: yellow) urine that was 2+ bilirubin (normal: negative), and heme negative (normal: negative); liver enzymes, including alkaline phosphatase, ALT, and AST, at 465 IU/L (normal: 30-120 IU/L), 237 IU/L (normal: ≤ 35 IU/L), and 112 IU/L (normal: ≤ 36 IU/L), respectively, were elevated; and total and direct bilirubin were elevated at 18.5 mg/dL (normal: ≤ 1.0 mg/dL) and 11.4 mg/dL (normal ≤ 0.5 mg/dL), respectively. Acetaminophen levels were below therapeutic range, and a urine toxicology screen returned negative for all drugs tested. Hepatitis serologies were negative for hepatitis A IgM, hepatitis C antibody, and hepatitis B core IgM, S antigen, and S antibody.

The patient subsequently underwent an abdominal ultrasound to rule out other causes of hepatocellular injury, such as choledocholithiasis or malignancy. The ultrasound showed a heterogeneously hyperechoic liver, consistent with diffuse hepatocellular injury. Unexpectedly, the ultrasound also showed intra- and extra-hepatic biliary duct dilatation with common bile duct sludge, that was concerning for possible choledocholithiasis. A follow-up magnetic resonance cholangiopancreatography (MRCP) was performed, which confirmed the moderate intra- and extra-hepatic biliary duct dilatation, but also revealed cystic duct dilatation, mild dilatation of the pancreatic duct, and associated filing defects consistent with stricture and obstruction. Endoscopic retrograde cholangiopancreatography (ERCP) was then performed with the goal of dilating the biliary and pancreatic ducts to alleviate the obstructive jaundice. The common bile duct was cannulated and stented, and a sphincterotomy was performed; however, there were no stones present. This common bile duct stricture was concerning for a malignant neoplasm, so brushings of the stricture were taken for cytology. The patient then underwent an abdominal CT, but no masses were identified near the stricture in the common bile duct or the pancreas. The cytology report showed atypical ductal pancreaticobiliary cells. During this period, the patient's elevated liver enzymes continued to down-trend until they were again within normal limits, and urinalysis also returned to within normal limits. Approximately two weeks after her initial presentation, the patient subsequently underwent a successful pancreaticoduodenectomy (Whipple procedure) for the surgical resection of a moderately differentiated adenocarcinoma of the common bile duct and carcinoma *in situ* of the cystic duct.

Discussion

Cascara sagrada belongs to a group of herbal supplements known as the anthranoid laxatives, that is commonly used for the treatment of constipation, and includes the well-known cathartic senna.[1,13] The primary chemical component of these supplements believed to be responsible for their cathartic effects is an anthracene-based molecule, typically an anthrone, anthraquinone, or dianthrone, that is metabolized in the intestine by local microflora to produce an aglycone anthranoid compound that stimulates intestinal motility and secretory activity.[1,13] While these supplements are typically believed to be relatively benign, over the past 15 years, several cases of hepatotoxicity have been linked to these supplements when used for a period of days to months. In these cases, patients presented with clinical features of hepatitis, including abdominal pain, jaundice, clay-colored stools, darkening urine, and elevated transaminase levels, which resolved following discontinuation of the offending supplement.[2-8] The patient described above presented to her primary care physician with similar symptoms, including fatigue, generalized jaundice, clay-colored stools, and darkening urine following the use of a supplement containing *Cascara sagrada* for the treatment of constipation.

Drug-induced liver injury (DILI) is the probable diagnosis in the patient who presents with signs and symptoms of acute liver injury following ingestion of high doses of a medication or herbal supplement. However, it is important to realize that DILI is a diagnosis of exclusion. Included in the differential diagnosis for DILI are acute viral hepatitis, autoimmune hepatitis, ischemic liver injury, alcoholic liver disease, genetic disorders such as Wilson's disease, and hepatobiliary malignancy. A detailed history, laboratory workup, and hepatobiliary imaging are invaluable in the diagnosis of this condition. Appropriate diagnostic laboratories and imaging include viral hepatitis serologies, autoimmune hepatitis serologies, medication levels, liver enzymes, complete blood count, and abdominal ultrasonography with or without liver biopsy.[9] The case described above provides an example of the importance of hepatobiliary imaging in the workup of DILI. While abdominal ultrasound showed diffuse hepatocellular injury, which is consistent with DILI, this imaging also identified biliary tract dilatation and cholestasis suggestive of a distal obstruction that would ultimately be diagnosed as an extrahepatic cholangiocarcinoma.

Cholangiocarcinomas are hepatobiliary malignancies derived from ductal epithelial cells of the biliary tree, and may be classified as intrahepatic or extrahepatic, depending on whether they are localized to the liver proper. Although a rare form of malignancy, accounting for approximately 3% of all gastrointestinal cancers, they are the most common cancer to arise in the biliary tree, and the second most common primary hepatic cancer.[10] The average incidence of cholangiocarcinoma in the United States is 1-2 cases per 100,000 persons per year. The highest rate of prevalence occurs in people in their seventh and eighth decades of life, and is more frequently diagnosed in males than females.[10-12] Due to the rarity of this malignancy, few risk factors for cholangiocarcinoma have been identified. Known risk factors include primary sclerosing cholangitis, chronic ulcerative colitis (an independent risk factor for primary sclerosing cholangitis), infection with liver flukes, chronic viral hepatitis, congenital fibropolycystic liver disease, bile duct cysts, and hepatolithiasis.[10-12]

Cholangiocarcinoma typically presents at an advanced stage. The symptoms a patient presents with will depend on the location of the tumor. In patients with extrahepatic cholangiocarcinomas, like that diagnosed in the case described above, most will present with obstructive jaundice. Patients with intrahepatic cholangiocarcinomas will typically present with abdominal pain. Other common symptoms include weight loss, clay-colored stools and darkening urine due to biliary tract obstruction, pruritus due to elevated bile acid levels, and fat malabsorption due to a paucity of bile acids in the digestive tract.[11,14]

Diagnostic workup for a patient with suspected cholangiocarcinoma should include a complete blood count, electrolytes, liver function tests, and imaging. Typical laboratory findings associated with extrahepatic cholangiocarcinomas include elevated direct bilirubin, ALP, and γ-glutamyltransferase, which are characteristic of pathologies arising in the biliary tract. Tumor markers such as CA 19-9 and carcinoembryonic antigen are frequently used in the diagnosis of cholangiocarcinoma, but have low sensitivity and specificity. It is important to note that

laboratory workup may produce results similar to that observed in a patient with choledocholithiasis, thus use of abdominal ultrasonography is important for excluding cholelithiasis.[14] Computed tomography may also be used to visualize the tumor, detect regional lymphadenopathy, and help to assess local resectability.[11] Magnetic resonance cholangiopancreatography may be used for the same purpose. Endoscopic retrograde cholangiopancreatography (ERCP) can be used to visualize the site of obstruction, and acquire samples for histopathological analysis, including brush cytology, biopsy, needle aspiration, and shave biopsies. A stent may also be placed during ERCP to relieve biliary obstruction.[11,14]

Treatment for cholangiocarcinomas depends on the stage of the disease, which is determined by the American Joint Committee on Cancer's tumor-node-metastasis staging algorithm for cholangiocarcinoma. The only potentially curative treatment for cholangiocarcinoma is surgical resection. However, as a majority of cholangiocarcinomas present at an advanced stage, surgical resection is often not an option.[14] Medical management in patients with unresectable, recurrent, or metastatic cholangiocarcinoma includes chemotherapy, typically gemcitabine, 5-fluorouracil, a platinum-based agent, or docetaxel, and palliative radiation therapy.[11]

Conclusions

Liver injury resulting from the use of anthranoid laxatives such as *Cascara sagrada* can produce symptoms that mimic the presentation of extrahepatic cholangiocarcinoma, including jaundice, pruritus, clay-colored stools, and darkening of urine. Thus, even in the presence of an acute hepatotoxic insult, malignancy should remain high in the differential diagnosis for an elderly patient who presents with this constellation of symptoms and lacks primary risk factors for cholangiocarcinoma.

Conflict of Interest

None of the authors identify a conflict of interest.

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