Subacute cholestatic hepatitis likely related to the use of senna for chronic constipation

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Abstract

We report a case of senna-induced cholestatic hepatitis which was not diagnosed at presentation. A 77 year old male was referred with abdominal pain, jaundice and elevated transaminase levels. A diagnosis of extrahepatic cholestasis was first suspected, due to the observation of a duodenal diverticulum and dilated proximal choledocus. However, the sphincterotomy did not improve cholestasis. At further evaluation, HBsAg was positive but serological work up was compatible with a healthy-carrier status. Further interrogation of the patient revealed a history of chronic senna intake to treat a chronic constipation. Liver biopsy showed bridging hepatocellular necrosis as well as canalicular cholestasis. Drug withdrawal resulted in a slow and progressive reduction in bilirubin levels and liver enzymes. In this case senna was likely the cause of a subacute cholestatic hepatitis exemplifying again the potential role of herbal related liver injury. (Acta gastroenterol. belg., **2005**, 68, **385-387**).

Key words : herbals**,** toxic hepatitis.

Introduction

There has been growing interest over the use of herbal medications. However, not all natural products are harmless and hepatotoxicity may be the most frequent life threatening adverse reaction due to herbal compound (1). One of the conditions in which herbal remedies are widely used is chronic constipation. Although "stimulant" laxatives are only recommended for short term use, many people with chronic constipation use them without professional advice for longer periods of time.

In this observation a case of senna induced toxic hepatitis is presented in which jaundice and the presence of a duodenal diverticulum first misguided the clinical investigation towards extrahepatic obstruction.

Case report

A 77 year old male was hospitalized with fatigue, abdominal pain and jaundice. He stated that his symptoms had been present for two weeks. He had no disease history, other than a lumbar discectomy operation. He was an ex coalminer and a former heavy smoker, of which he quitted 15 years ago. He was a teetotaller and had no history of toxic chemical intake. He had been habitually taking an herbal laxative, sennoside, 15-30 mg/day for more than three months to treat chronic constipation.

Physical examination revealed a sick appearing elderly male with icteric sclerae and a tender right upper quadrant. Cardiac examination disclosed pansystolic high grade systolic murmurs on each quadrant and bilateral fine crackles on lower chest.

He had a normal complete blood count and elevated transaminase, bilirubin, ALP and GGT levels (AST : 481 IU/L, ALT : 657 IU/L, conjugated bilirubin : 2.75 mg/dl, unconjugated bilirubin : 2.16 mg/dl, ALP : 160 IU/L, GGT 237 IU/L). Serum glucose, total cholesterol, creatinin levels were within the normal limits. HbsAg was positive with a status of chronic nonreplicating HBV (HbsAg : Positive, Anti HBc IgG : Positive, HbeAg : Negative, Anti-HBe : Positive, HBV DNA PCR : Negative), Anti HCV antibodies were negative. Other than biliary sludge in the gallbladder, abdominal ultrasound showed normal liver sonogram, and normal extrahepatic biliary system.

A week later, the liver enzymes remained in the same range (AST : 449 IU/L, ALT : 507 IU/L), serum bilirubin however rising with conjugated bilirubin (7,1 mg/dl) far exceeding the unconjugated fraction (3,8 mg/dl). Abdominal ultrasound examination was unchanged. Magnetic resonance cholangiopancreatography (MRCP), showed an enlargement of the proximal choledochus. At endoscopic retrograde cholangiopancreatography (ERCP), the ampulla was distal from a diverticulum with a 12-15 mm orifice and the choledochus was found to be enlarged while the intrahepatic biliary tract and gallbladder were normal. The procedure was terminated by sphincterotomy to decrease the risk of stasis and cholangitis. However, the jaundice persisted despite the procedure. Transaminase levels slightly decreased (AST : 325 IU/L, ALT : 397 IU/L), however with a total bilirubin level continuing to rise (conjugated : 12 mg/dl, unconjugated : 2 mg/dl). On the 6th day post-sphincterotomy, total bilirubin level was 16,9 mg/dl (conjugated 14 mg/dl, unconjugated 2,9 mg/dl). The liver enzyme levels reached AST 145 IU/L, ALT 104 IU/L.

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FIGURE 1 MANQUE !

Fig. 1. — An enlarged and inflamed portal tract

FIGURE 2 MANQUE !

Fig. 2. — Parenchymal inflammation with ballooning

Screening of other factors potentially responsible for hepatocellular injury was completed. Autoantibodies (antinuclear antibodies, anti-smooth muscle antibodies, and liver-kidney microsomal antibodies), alpha1 antitrypsin and caeruloplasmin levels were found to be normal. His only ongoing medication at the time of referral was an herbal medication, sennoside, which he had been taking 3-4 tablets a day (15-30 mg/d) for more than 3 months due to his chronic constipation. He admitted that he occasionally took senna tablets even after hospitalization despite medical recommendation.

A liver biopsy was performed. Histopathological examination showed enlarged portal tracts with a predominantly lymphocytic inflammatory infiltrate. Widespread piecemeal necrosis and areas of bridging necrosis were present. There was parenchymal disarray with marked hepatocellular ballooning and Councilman bodies accompanied by marked inflammation dominated by polymorphic neutrophils. Acinar transformation of hepatocytes accompanied canalicular cholestasis which was present throughout the specimen. Reticulin network was collapsed in some places. The picture was compatible with acute cholestatic hepatitis (Fig. 1 and 2).

The patient was strictly recommended not to take any medication and during follow up, bilirubin levels and liver enzymes gradually decreased to near normal levels. In the 1st month of his discharge, serum bilirubin and liver enzymes were all within normal levels.

Discussion

There is a widely shared misconception that herbal medicines are harmless, since they are of natural origin. However, this concept has been challenged recently by the publication of several reports of an association between herbal drugs and toxicity (1,2). While most of the adverse effects on the digestive system have been self-limiting and relatively inconsequential, the same is not true for herb-induced hepatotoxicity, in which fatalities have been reported with an alarming frequency (2). The growing number serious adverse effects reports of herbal remedies on the liver include a variety of patterns of liver injuries, from acute and chronic hepatitis to fulminate hepatic failure (3,4). Chaparral, germander, mistletoe, valerian root, skullcap, senna, jin bu huan, atractylis, and pyrrolizidine alkaloids been implicated as relatively more frequent causes of liver dysfunction (5).

Herbals are commonly used in the traditional symptomatic approach to management of constipation. Despite many reports about the hepatotoxicity of numerous herbals, only rare cases of hepatic inflammation induced by anthraquinone derivatives have been reported (6,7). It is suggested that anthraquinone might be metabolized in the intestines to form highly reactive anthrones that, when absorbed and transported into liver, result in reversible liver damage (8). In our literature search for “senna induced hepatotoxicity” we found only one case report of a patient with pericentral hepatitis after use of a large dose of senna (9). Senna is known to be a relatively safe drug in comparison to other herbals. In a small sample study of elderly patients with chronic constipation, 20 mg sennosides daily was administered for six months without any adverse effects (10).

In the evaluation of the current case, senna intake could have been elucidated more readily. However, the diagnosis was delayed because of incomplete clinical

interview and confounding clinical findings misleading us towards extrahepatic cholestasis. Drug-induced cholestasis may occur mostly in a dose-related fashion, or occasionally as an idiosyncratic or allergic reaction. Hepatocellular injury caused by drugs or toxins may eventually present as a predominantly cholestatic syndrome (11). Once hepatotoxicity develops, sustained use of the offending product greatly increases morbidity (12,13). In the face of ongoing hepatotoxicity, continued ingestion of the herbal preparation may lead to cirrhosis or fulminant hepatic failure (14). Therefore, it is imperative in every patient with cholestasis to carefully investigate the current and past medication history including over-the-counter compounds.

In our case morphology of the liver was compatible with severe acute injury with cholestasis. Although those findings were not specific, clinical presentation and evaluation as well as other laboratory findings indicated that senna related liver injury was likely the cause. Regression of clinical and laboratory findings after withdrawal of the herbal compound was another indirect proof for the diagnosis.

In conclusion, herbal remedies must be considered as a potential etiologic agent while investigating all types of liver injuries. The mainstay of therapy for herbal hepatotoxicity is the immediate withdrawal of the offending drug.

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