Case Report: Drug Toxicity Leading to Vanishing Bile Duct Syndrome and Cholestatic Jaundice

D Marks

Citation

D Marks. *Case Report: Drug Toxicity Leading to Vanishing Bile Duct Syndrome and Cholestatic Jaundice*. The Internet Journal of Gastroenterology. 2008 Volume 8 Number 1.

Abstract

A 37 year old black woman is described with difficult-to-control diabetes (DM), morbid obesity, hypertension, and chronic skin abscesses. During admission for control of skin abscesses, she received trimethoprim-sulfamethoxazole (TMP-SMZ), which was continued for 30 days after discharge. She then required admission for UTI and was treated with antibiotics. Metformin and glimepiride were added at the time of discharge, as parenteral insulin was poorly controlling the DM. Shortly thereafter she developed a cholestatic drug reaction, which progressed to end-stage liver disease (ESLD) with the histologic features of vanishing bile duct syndrome (VBDS). Clinical characteristics of medication-induced cholestatic liver disease and VBDS are discussed.

CLINICAL COURSE:

5/9/06 hospitalized for incision and drainage of buttock abscess. She did not smoke, nor consume alcohol. She denied use of herbal medications or anabolic steroids. There was no history of IV drug abuse or tattoo. There was a family history of DM, but not of liver disease. Discharge medications included TMP-SMZ. Liver enzymes were normal.

6/5/06 admitted for 2-3 day history of throat pain, non-productive cough, fever and chills. Medications on admission included Novolin 70/30 30 units qam and 20 units qpm, and TMP-SMZ since 5/9/06. Vital signs: BP 113/66, temperature 36.8 C, heart rate 100, respiratory rate 16. Labs indicated WBC 5.9, Hgb 11.4, glucose 265, AST 131, ALT 72, alkaline phosphatase 152. Evaluation for the abnormal liver enzymes showed an unremarkable hepatitis panel; ultrasound revealed gallstones and a contracted gallbladder; and the hepatobiliary scan was normal. Treatment was started with piperacillin and tazobactam combo for presumed UTI, and she was discharged shortly thereafter. Discharge meds included levofloxacin, clindamycin, sliding scale insulin and an ADA diet. Oral hyopglycemics (metformin and glimepiride) were also started. An elective laparoscopic cholecystectomy was performed due to gallstone.

7/20/06 admitted for methicillin-resistant Staph. aureus infection of buttock abscess.

9/7/06 admitted for control of back abscess and generalized itching. DM was noted to be out of control.

9-16-06 re-admitted for shortness of breath, uncontrolled blood sugars, itching, yellow eyes for three days, and 25 pound weight loss. Patient stated that her stools had a light color and her urine appeared dark. Meds on admission included: glucophage, glimepiride, diphenhydramine, levofloxacin and clindamycin. On exam, the patient did not show organomegaly, abdominal mass or tenderness; ocular jaundice was present, and labs values were glucose 383, AST 208, ALT 227, alkaline phosphatase 1004, bilirubin 14, albumin 2.9, INR 1.05, PTT 30.3. No evidence of bile tract dilatation was seen on MR cholangiopancreatography, but multiple cholelithiasis was present. Novolin insulin was changed to Lantus insulin, and oral hypoglycemics (metformin and glimepiride) were discontinued. A consult from gastroenterology service opined that the biochemical abnormalities pointed toward an obstructive etiology.

9/19/2006 MR cholangiopancreatography showed cholelithiasis but no evidence of bile tract dilatation. An ERCP was performed, and the pancreatic and bile ducts appeared normal, with no signs of obstruction, stones or sludge; a sphincterotomy was performed. On 10/9/2006 the consulting hepatologist felt that the underlying pathology was cholestatic jaundice of uncertain etiology, but most likely due to a drug reaction to glimepiride. A liver biopsy on 10/12/2006 showed an overall preservation of hepatic

architecture.

Patient continued to have severe jaundice and disabling pruritis, without signs or symptoms of decompensated liver disease. On 10/19/2006 her liver enzymes remained elevated: AST 279, ALT 197, alkaline phosphatase 925, total bilirubin 17.1, albumin 2.3, direct bilirubin 10.5, indirect bilirubin 6.6.

12/14/06 liver consult opined that Ms. W had a bland (acute choestatis without hepatocellular or bile duct injury), drug-induced cholestatic reaction. This has been reported with the sulfonylureas and was felt likely related to glimepiride. A liver biopsy was recommended if jaundice persisted for another 2-3 months, to exclude idiopathic ductopenia.

1/25/2007 the consulting hepatologist recommended a repeat liver biopsy to exclude VBDS, because of its association with persistent cholestatic injuries in the setting of a drug reaction. On 2/5/2007 a liver biopsy showed histologic findings of VBDS. The hepatologist (3/8/07) stated that although hepatic-synthetic function was well-preserved, the drug-induced (which he attributed to glimeperide) liver injury would not improve.

3/14/2007 evaluated for liver transplant, and found to have ESLD secondary to cholestatic liver injury secondary to drug reaction. She eventually underwent an orthotopic liver transplant (OLT) on 5/15/07.

DISCUSSION

Ms. W's initial clinical course was characteristic for medication-induced cholestatic liver disease. Typically, slow resolution should occur with discontinuation of the offending drug. When recovery did not occur as expected, the presence of VBDS was identified, leading to liver transplant.

Cholestatis is a syndrome resulting in reduced bile flow. Mechanisms are either 1) hepatocellular, where an impairment of bile formation occurs, or 2) obstructive, where impedance to bile flow occurs after it is formed. The typical histopathologic features of hepatocellular cholestasis include the presence of bile within hepatocytes and canalicular spaces, in association with generalized cholestatic injury. Obstructive cholestasis, which was not present in this case, is characterized by bile plugging of the interlobular bile ducts, portal expansion, and bile duct proliferation in association with centrilobular cholestatic injury.

In both hepatocellular and in obstructive cholestatic disease, the bilirubin is elevated (Kaplan; Schiff). Hepatocellular injury is often accompanied by aminotransferase >500 and alkaline phosphatase level normal to 3x upper limit of normal (uln). In obstructive injury, the aminotransferase is normal to mildly elevated, and alkaline phosphatase can be up to 4x uln, which was the pattern seen on 9/16/06. Another feature of the case pointing her treating and consulting physicians toward an obstructive picture was the finding of multiple gallstones.

Causes of hepatocellular cholestasis include:

Viral hepatitis (A, B or C),

Alpha 1-Antitrypsin Deficiency,

inborn errors of bile acid synthesis

Total parenteral nutrition (TPN)–associated cholestasis

Drug-induced cholestasis –Some common drugs associated with cholestatic injury include amoxicillin-clavulanic acid, chlorpromazine, ciprofloxacin, ofloxacin, cimetidine, phenytoin, naproxen, captopril, erythromycin, azithromycin, and dicloxacillin. Sulindac or octreotide can lead to extrahepatic cholestasis secondary to biliary sludge or calculi. In this case, there was no biliary sludge of obstructing calciul seen by ERCP

Causes of obstructive cholestasis include:

Progressive familial intrahepatic cholestasis,

Biliary atresia,

Congenital bile duct anomalies (Choledochal Cysts) ,

Cholelithiasis,

Primary Sclerosing Cholangitis,

Infectious cholangitis,

Cholangitis associated with Langerhans Cell Histiocytosis,

Cholestasis with ductal paucity,

Alagille Syndrome,

Nonsyndromic ductal paucity,

Ductopenic allograft rejection,

VBDS.

Initially, this patient's workup seemed to indicate a hepatocellular mechanism for the jaundice, as the cause was felt to be drug-induced. She had been started on both TMP-SMZ and glimepiride around the same time several months before her problem manifest clinically, and both have been reported associated with cholestatic jaundice.

VBDS is a rare disorder, affecting the intrahepatic bile ducts (Schiff; Sleisenger; Yao). Most patients are asymptomatic, but some may present with pruritus and, rarely, jaundice. The alkaline phosphatase level usually is elevated, along with GGT, which may exceed 600 IU/L. Obtaining a wedge biopsy of the liver often is necessary to make the diagnosis. On physical examination, frontal bossing and triangular facies may be noted, and additional tests can reveal butterfly vertebrae and posterior embryotoxon of the eye, but these findings were not present for this patient. Alagille Syndrome and progressive familial intrahepatic cholestasis can also lead to VBDS, as can cystic fibrosis, systemic mastocytosis, histiocytosis-X, and Hodgkin disease, but some cases remain idiopathic. VBDS has been reported in association with the following medications: chlorpromazine,flucloxacillin, amitriptyline and TMP-SMZ.

Both TMP-SMZ and glimepiride had a temporal association with this patient’s cholestatic jaundice. TMP-SMZ but not glimepiride has been reported to be a causally related to VBDS. Using standard accepted methods of determining causation (Marks 200) TMP-SMZ, the common denominator for both the cholestatic jaundice and subsequent VBDS was probably causative.

In summary, a case is presented with medication-induced cholestatic jaundice progressing to VBDS. Although the biochemical markers pointed to an obstructive etiology, in this case the cholestatis was drug-induced (TMP-SMZ) but of an obstructive nature. Physicians prescribing the commonly used medications described in this paper should always consider the possibility of medication-induced liver disease when liver enzymes become abnormal, and immediately withdraw any potentially offending agents if necessary.

References

r-0. Amaryl. (2008). Physicians’ Desk Reference. Thomson Healthcare, Inc.: Montvale, NJ.
r-1. Bactrim. (2008). Physicians’ Desk Reference. Thomson Healthcare, Inc.: Montvale, NJ.
r-2. Farewell, GC (ed) The clinicopathological spectrum of drug-induced liver diseases. Drug-induced liver disease, Churchill Livingstone, London, 1994
r-3. Goodman & Gillman, Pharmacologic Basis of Therapeutics, 11th ed.,
r-4. Kaplan M. Evaluation of hepatobiliary diseases. In: Stein JH, ed. Internal Medicine. Boston: Little, Brown, 1990:443.
r-5. Marks, D.H. (2005). Evaluation of medical causation, in Drug Injury: Liability, Analysis and Prevention, Second Edition, Chapter 10. O’Donnell JT editor. L&J Publications, 2005
r-6. Sitruk V, Mohib S, Grando-Lemaire V, Ziol M, Trinchet JC. [Acute cholestatic hepatitis induced by glimepiride] Amaryl. Gastroenterol Clin Biol. 2000 Dec;24(12):1233-4; in French.
r-7. Schiff ER. (ed). Diseases of the Liver, 9th ed. 2003. Lippincott, Williams, Wilkins.
r-8. Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management, 2006.
r-9. Yao F, Behling CA, Saab S, Li S, Hart M, Lyche KD. Trimethoprim-sulfamethoxazole-induced vanishing bile duct syndrome. Am J Gastroenterol. 1997 Jan;92(1):167-9.

Author Information

Donald H. Marks, MD, PhD
Cooper Green Mercy Hospital (CGHM), Director of Hepatitis Clinic, and Pharmacy and Therapeutics Committee, Birmingham, Alabama