ACG CASE REPORTS JOURNAL

CASE REPORT | LIVER

Vanishing Bile Duct Syndrome Associated With Estrogen

John Benfield, MD[1], Raj A. Shah, MD[2], Douglas J. Grider, MD[3,4], and Farhad Sahebjam, MD[1,2]

[1]*Department of Internal Medicine, Virginia Tech Carilion School of Medicine, Roanoke, VA*
[2]*Division of Gastroenterology, Department of Internal Medicine, Virginia Tech Carilion School of Medicine, Roanoke, VA*
[3]*Department of Basic Science Education, Virginia Tech Carilion School of Medicine, Roanoke, VA*
[4]*Dominion Pathology Associates, Roanoke, VA*

ABSTRACT

Vanishing bile duct syndrome (VBDS) refers to a form of cholestatic liver disease with many etiologies. Vanishing bile duct syndrome is characterized by biliary ductopenia and chronic cholestasis. This is a challenging condition for clinicians because of its rarity and unclear pathophysiology. Presented is an 18-year-old woman who developed cholestatic liver injury and intrahepatic biliary ductopenia after a course of oral contraceptives and intravenous estrogen for uterine bleeding. A year later, this patient did not have significant improvement in liver biomarkers and was referred for transplantation.

INTRODUCTION

Biliary ductopenia is characterized by a paucity of intrahepatic bile ducts, specifically the loss of 50% or more portal tracts.[1] Vanishing bile duct syndrome (VBDS) is a form of cholestatic liver disease arising from multiple etiologies that is characterized by biliary ductopenia. The finding has been attributed to a variety of pathologic processes that include Hodgkin lymphoma, human immunodeficiency virus, and drug-induced liver injury (DILI).[2]

Cholestatic liver injury has frequently been associated with estrogen use. The likely mechanism occurs through changes in bile metabolism due to modulation by estrogen of various receptors that include bile salt export pump (BSEP) and multidrug resistance-associated protein 2.[3] However, on reviewing the literature, there has been no previously reported case of VBDS occurring secondary to the administration of estrogen therapy.

CASE REPORT

An 18-year-old woman with a medical history of alpha-gal syndrome and dysfunctional uterine bleeding initially presented with a report of vaginal spotting, which was attributed to a previously implanted intrauterine device. The device was removed, and she was prescribed daily oral contraception composed of norethindrone 1 mg, ethinyl estradiol 20 μg, and ferrous sulfate 75 mg. Twelve days later, she was admitted to the hospital for continued vaginal bleeding. She received 75 mg of intravenous conjugated estrogens. Her symptoms improved overnight, and she was discharged the following day. She received a prescription of estradiol 2 mg 3 times daily and medroxyprogesterone 10 mg daily, followed by norgestimate and ethinyl estradiol tablets daily.

Two weeks later, she presented to the emergency department complaining of 3 days of pruritus, abdominal pain, conjunctival icterus, and dark urine. Aminotransferase levels are graphed in Figure 1. Preceding this presentation, aminotransferase levels were last obtained 4 years earlier and were used to establish the baseline. She denied any diagnosis of liver disease in the intervening years. She was treated with cholestyramine and hydroxyzine and referred to a hepatology clinic for further assessment.

ACG Case Rep J 2022;9:e00776. doi:10.14309/crj.0000000000000776. Published online: May 5, 2022

Correspondence: John Benfield, MD (jwbenfield@carilionclinic.org).

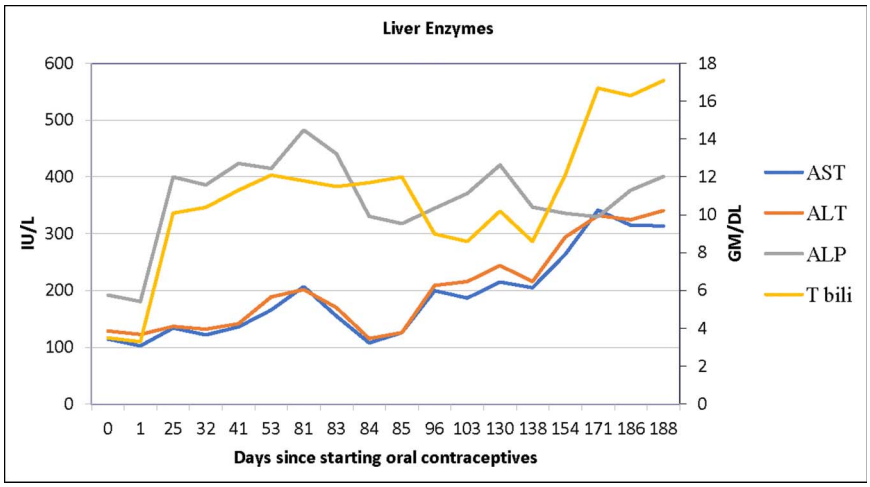

Figure 1. Graph of levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and total bilirubin (T bili). Day 0 indicates the start of oral contraceptive therapy. Values corresponding to day 0 were obtained 4 years before presentation and were within the normal range of values according to our laboratory.

Oral contraceptives were stopped on the first hepatology clinic visit. She had no history of use of alcohol, illicit drugs, or herbal remedies. The workup for viral hepatitis (A, B, C, E, cytomegalovirus, and Epstein-Barr virus) was negative. Autoimmune studies were obtained to rule out primary biliary cholangitis and autoimmune cholangitis. These revealed the presence of antinuclear antibodies; however, antimitochondrial and anti-smooth muscle antibodies were not found. Magnetic resonance cholangiopancreatography was unremarkable. Subsequent endoscopic ultrasound found no gallstones, and an endoscopic ultrasound-guided transgastric core biopsy of the liver was obtained 1 month after her presentation with cholestatic liver injury. Histology showed acute and chronic cholestasis and nearly complete loss of bile ducts with prominent biliary metaplasia of hepatocytes, as shown in Figures 2 and 3.

Cholestyramine was stopped because there was no improvement of itching despite dose escalation. Diarrhea improved with low-fat diet. She was prescribed ursodeoxycholic acid but without clinical or laboratory improvement. She has been referred for liver transplantation because of the progressive nature of her liver injury.

DISCUSSION

DILI is generally categorized as either immune-mediated or non-immune-mediated. The biochemical pattern of liver injury

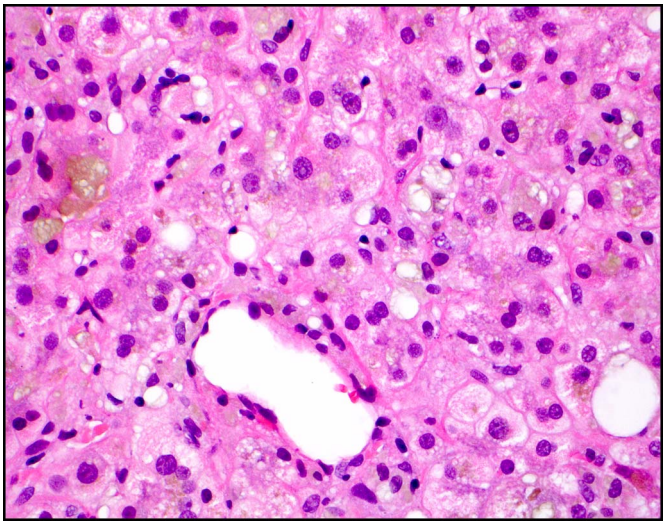

Figure 2. Transgastric liver biopsy stained with hematoxylin and eosin, 40× magnification. There were 5 portal areas present in fragmented needle core biopsies. Only remnants of a single bile duct were noted in 1 portal tract, and this bile duct was not intact. All the other portal areas were missing bile ducts.

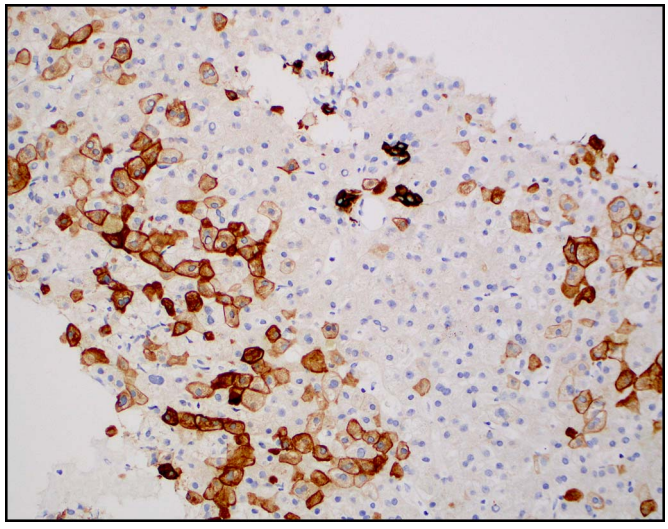

Figure 3. Transgastric liver biopsy stained for CK7, 20× magnification. CK7 is expressed by bile ducts and bile ductular epithelial cells. CK7 positivity in hepatocytes supports biliary metaplasia of hepatocytes, a prominent response to bile duct injury.

has also been used to differentiate DILI into hepatocellular, cholestatic, or mixed disease.[4] Cessation of the offending drug leads to resolution of injury in most cases, but cholestatic drug injury may rarely lead to persistent VBDS.[1] The mechanism by which cholestatic liver injury can lead to VBDS remains a topic of investigation.

Estrogen is a relatively common cause of cholestatic liver injury, including intrahepatic cholestasis of pregnancy. There is a paucity of data regarding the progestin-related cholestatic liver injury. Estrogens are metabolized by conjugation and then excreted into the biliary system. Cholestasis induced by estrogens is likely to be caused by action on bile transport at the canalicular membrane of hepatocytes. Estrogen-induced cholestasis is not explained by inhibiting entry of bile acids into hepatocytes.[5]

Beta-estradiol 17-(beta-D-glucuronide) (E217G) is a metabolite of estradiol that is transported into intrahepatic bile ducts by multidrug resistance-associated protein 2. E217G inhibits BSEP from the canalicular aspect.[6] BSEP is responsible for the transport of bile salts from the hepatocyte to bile canaliculi.[6] Loss of function of this protein, as observed in progressive familial intrahepatic cholestasis type 2, can result in severe cholestatic injury,[7] thereby providing a rationale for cholestasis caused by E217G. Inhibition of bile transport into the canaliculus as the mechanism of cholestasis is corroborated by hepatocellular accumulation of bile in our patient's liver biopsy. The mechanism of the development of ductopenia is not well understood. Cholestatic injury to bile ductules may increase apoptosis of those ductules or decrease regeneration.[2,8] Bile duct regeneration involves progenitor cells found in the finer branches of the biliary tree. The loss of the finer branches of the biliary tree has been implicated in bile duct loss in chronic liver rejection.[9]

The prognosis of VBDS is variable. In a review of case reports of VBDS resulting from DILI, 39 cases were found, with poor outcomes in 15 cases; these outcomes include chronic liver disease, cirrhosis, liver transplantation, and death. Death occurred in 4 cases.[10] Effective treatment of cholestatic DILI with persistent VBDS has been elusive. Ursodeoxycholic acid may enhance bile acid secretion and inhibit cholangiocyte apoptosis.[11] Immunosuppressive agents may be used to reduce ongoing inflammation. However, treatment in these cases is generally supportive and focuses on symptoms of cholestasis, including pruritus and steatorrhea. Cholestyramine is often used to relieve pruritus in these patients but may exacerbate malabsorption. Antihistamines, ursodeoxycholic acid, opiate antagonists, plasmapheresis, and phototherapy may be used to address pruritus.

Although estrogen use has been associated with cholestatic DILI, no case has yet been reported of VBDS secondary to estrogen on our review of the literature. The Roussel Uclaf Causality Assessment Method score is 6 indicating that the use of oral and intravenous estrogen was the probable cause of DILI and consequent VBDS.[12] VBDS remains a challenging condition because of its rarity and our limited understanding of its pathophysiological underpinnings. Insights into the mechanisms of bile duct destruction in VBDS may reveal therapeutic targets to stop bile duct destruction before the disease becomes severe.

DISCLOSURES

Author contributions: J. Benfield, RA Shah, DJ Grider, and F. Sahebjam wrote and edited the manuscript. DJ Grider provided the images. J. Benfield is the article guarantor.

Financial disclosure: None to report.

Informed consent was obtained for this publication.

Received June 8, 2021; Accepted December 8, 2021

REFERENCES

1. Ludwig J. Idiopathic adulthood ductopenia: An update. *Mayo Clin Proc*. 1998;73(3):285–91.
2. Reau NS, Jensen DM. Vanishing bile duct syndrome. *Clin Liver Dis*. 2008; 12(1):203–17.
3. Chen J, Zhao KN, Liu GB. Estrogen-induced cholestasis: Pathogenesis and therapeutic implications. *Hepatogastroenterology*. 2013;60(126):1289–96.
4. Katarey D, Verma S. Drug-induced liver injury. *Clin Med*. 2016;16(Suppl 6): S104.
5. Brock WJ, Durham S, Vore M. Characterization of the interaction between estrogen metabolites and taurocholate for uptake into isolated hepatocytes. Lack of correlation between cholestasis and inhibition of taurocholate uptake. *J Steroid Biochem*. 1984;20(5):1181–5.
6. Stieger B, Fattinger K, Madon J, Kullak-Ublick GA, Meier PJ. Drug-and estrogen-induced cholestasis through inhibition of the hepatocellular bile salt export pump (Bsep) of rat liver. *Gastroenterology*. 2000;118(2):422–30.
7. Bull LN, Thompson RJ. Progressive familial intrahepatic cholestasis. *Clin Liver Dis*. 2018;22(4):657–69.
8. Nakanuma Y, Tsuneyama K, Harada K. Pathology and pathogenesis of intrahepatic bile duct loss. *J Hepatobiliary Pancreat Surg*. 2001;8(4):303–15.
9. Van den Heuvel MC, de Jong KP, van der Horst ML, Poppema S, Slooff MJ, Gouw AS. Impaired regeneration of biliary cells in human chronic liver allograft rejection. Special emphasis on the role of the finest branches of the biliary tree. *Liver Transpl*. 2004;10(1):28–35.
10. Wasuwanich P, Ingviya T, Karnsakul W. 508–Clinical outcome in individuals with vanishing bile duct syndrome from drug induced liver injury. *Gastroenterology*. 2019;156(6):S-1204.
11. O'Brien CB, Shields DS, Saul SH, Reddy KR. Drug-induced vanishing bile duct syndrome: Response to ursodiol. *Am J Gastroenterol*. 1996;91(7): 1456–7.
12. Benichou C, Danan G, Antoine F. Causality assessment of adverse reactions to drugs—II. An original model for validation of drug causality assessment methods: Case reports with positive rechallenge. *J Clin Epidemiol*. 1993; 46(11):1331–6.