A Case of Vanishing Bile Duct Syndrome

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CASE PRESENTATION

A 75-year-old Haitian man presented to the emergency department (ED) with altered mental status (disoriented to time and place). Although a poor historian, he did report progressive worsening of vision in his eyes bilaterally over an approximate 2-week period. Past medical history included type 2 diabetes mellitus for approximately 6 years and hypertension. He was not compliant with medications for these chronic conditions as prescribed by his primary care physician and was taking no medications at the time of assessment in the ED. Social history was significant for alcohol use of 1-2 beers per day for numerous years up until 3 months previously. He denied tobacco or illicit drug use.

Review of systems was positive for polyuria, polydipsia, and generalized weakness, as well as the visual changes. He denied chest pain, shortness of breath, orthopnea, headache, or abdominal discomfort. On physical examination, the patient was afebrile. He had decreased bilateral visual acuity, scleral icterus, and a pterygium in the left eye. The buccal mucosa was dry, and he had poor dentition. He had tachycardia, with a regular heart rate of 110 beats/min, and heart sounds were distant. He was also tachypneic, with a respiratory rate of 24, and bibasilar crackles. On abdominal examination, the patient had positive bowel sounds in all four quadrants, no hepatomegaly, and no pain, tenderness, or rebound elicited in any quadrants. His skin was jaundiced, dry, and intact. There was hyperpigmentation of his ankles bilaterally, but no ulcerations or bony deformities. Distal pulses were normal. On neurologic examination, he was awake and oriented x 1 (to person). Upper extremities revealed 5/5 muscular strength. Mild proximal lower-extremity weakness was evident at 4/5. Reflexes were normal throughout, as was dorsiflexion and plantar flexion.

The basic metabolic panel was within normal limits (WNLs). Sodium was borderline low at 132 mEq/L, but potassium, chloride, and carbon dioxide were WNLs. Renal compromise was evident, however, with blood urea nitrogen of 46 mg/dL and creatinine of 2.6 mg/dL. There were no previous levels with which to make a comparison. Glucose was elevated to 147 mg/dL. Albumin was low at 2.6 g/dL. On coagulation parameters, the partial thromboplastin time (PTT) was prolonged to 45 seconds. Erythrocyte sedimentation rate was only 5 mm/h. Liver function tests (LFTs) were elevated to the following: aspartate aminotransferase (AST) 151 U/L, alanine aminotransferase (ALT) 165 U/L, and alkaline phosphatase 572 U/L. A urinalysis showed protein 300 g/dL, glucose 250 mg/dL, large bilirubin, small blood, 2+ bac-
teria, 5-10 white blood cells, and trace ketones. A chest radiograph did not reveal any lung parenchymal abnormalities or infiltrates. A brain computed tomography (CT) scan showed bilateral white matter changes consistent with chronic microvascular disease.

The patient was diagnosed with two main problems on admission: delirium due to a urinary tract infection, and renal failure most likely prerenal in nature secondary to volume depletion. Orthostatics were borderline in the ED. The patient was hydrated with normal saline and started on levofloxacin. He was admitted to the acute geriatric unit, where his mental status improved, and he was placed on a sliding scale of regular insulin to control his diabetes. Nifedipine, and then a combination of metoprolol and minoxidil, were initiated to control hypertension. An ophthalmology consult was requested, and a diagnosis of glaucoma and mild diabetic retinopathy was later made. The patient was started on timolol and latanoprost/benzalkonium eyedrops, in addition to laser surgery being planned in the near future. A urine culture later came back with no growth, the infection likely having cleared with antibiotics before the culture was collected. Blood cultures were negative.

Follow-up studies during the patient’s hospital admission were as follows: hemoglobin A1C was elevated at 6.9% and urine microalbumin was high at 85 mg/L, suggesting diabetic nephropathy. The patient scored a 19/22 on the Mini-Mental State Examination and a 7/15 on the Geriatric Depression Scale (GDS) examination. Aspartate aminotransferase and ALT levels continued to progressively climb, however, reaching peak levels of 309 U/L and 292 U/L, respectively. Alkaline phosphatase increased as well to 733 U/L. Subsequently, attention was focused on the patient’s liver status and prolonged PTT, given his history of alcohol abuse.

Further blood work-up revealed these results: gamma-glutamyl transpeptidase (GGT) had increased following admission from 354 U/L to 701 U/L; alpha-fetoprotein was normal at 1 ng/mL; carcinoembryonic antigen was normal at 2.5; carbohydrate antigen (CA) 19-9 and CA 125 (both tumor markers) were significantly elevated at 334 U/mL and 162 U/mL, respectively. Antinuclear antibody (ANA) was negative. Ferritin was high at 1829 ng/mL, as was lactic dehydrogenase at 563 U/L, reticulocyte count at 3%, and vitamin B12 greater than 2100 pg/mL. Cytomegalovirus (CMV) IgM antibody was negative. Lipid profile only showed a high triglyceride level of 338 mg/100 mL. Amylase and lipase were WNLs.

A liver ultrasound was ordered to rule out biliary obstruction. Results were negative overall, revealing that the gallbladder was contracted and partially thickened. Liver size was WNLs at 13 cm; the common bile duct and spleen showed no abnormalities. At that point, it was decided that other etiologies should be ruled out, such as hepatitis and liver damage due to alcohol, toxic, or ischemic etiologies.

The elevated LFTs were believed secondary to intrahepatic cholestasis, and due to their increasingly worsening levels, a hepatology consult was requested. The subspecialty service considered the high LFTs to possibly be compatible with a drug effect (the patient did not remember previous medications he had been taking), cancer, or an infiltrative process. The overall unspecified picture appeared to be acute instead of chronic hepatocellular injury. Serologic tests for viral hepatitis were subsequently found to be negative.

Debate occurred over whether further work-up should include: a repeat of an abdominal ultrasound to specifically assess the liver’s portal vessels and rule out veno-occlusive disease; a triple-phase CT scan to
evaluate the liver, hepatic ducts, and head of the pancreas (which the renal service recommended against due to the patient’s acute renal failure and the risk posed by exposure to intravenous contrast); or a magnetic resonance imaging (MRI) scan of the abdomen with gadolinium that would provide the same information as the triple-phase CT scan. An MRI scan was eventually done in addition to magnetic resonance cholangiopancreatography (MRCP) that revealed 1 cm dilation of the distal common bile duct all the way to the head of the pancreas, consistent with intrahepatic abnormalities, but no intrahepatic biliary dilation or gallstones were detected.

Because of the MRCP findings, the gastrointestinal service performed an endoscopic retrograde cholangiopancreatogram (ERCP) to rule out a pancreatic or ampullary obstruction. Results showed intrahepatic duct attenuation consistent with a mass or sclerosing cholangitis, but normal common bile and pancreatic duct systems. Diagnosis at this point was intrahepatic cholestasis, requiring the condition vanishing bile duct syndrome (VBDS) to be ruled out.

Diagnosis

A liver biopsy was performed. The results found extensive damage of interlobular bile ducts. Portal fibrosis with focal bridging fibrosis was also present. Histologically, the damaged ducts were distorted and inflamed. In certain areas the ducts were atrophic, and in others they were focally absent. An inflammatory infiltrate was present, predominantly consisting of lymphocytes and some neutrophils. No abnormal iron stains were found to suggest hemochromatosis.

The biopsy was determined to be positive for vanishing bile duct syndrome, with ductopenia and portal tract fibrosis of unknown etiology. Given that the patient’s LFT levels were starting to come down (follow-up levels after peaking of AST and ALT were 182 U/L and 111 U/L, respectively) and that he was not in liver failure, the recommendation of conservative treatment was suggested by hepatology, using ursodiol in dosages from 300 mg to 1200 mg each day.

DISCUSSION

Vanishing bile duct syndrome (also known as idiopathic adulthood ductopenia or intrahepatic cholangiopathy) is a form of intrahepatic cholestasis that often presents with jaundice and pruritus. It is a rare condition in which there are a decreased number of bile ducts seen in liver biopsy specimens. The syndrome causes lesions of the biliary epithelium of interlobular ducts, which is the area most affected by immune-mediated damage, as occurs in hepatic allograft rejection (HAR), idiopathic jaundice with or without pruritus, adulthood ductopenia, primary biliary cirrhosis (PBC), or primary sclerosing cholangitis (PSC). Histologically, it is similar to PBC, where there is marked ductopenia in “burnt-out” portal areas with a small number of inflammatory cells.

Clinical manifestations

Typically, the syndrome starts abruptly with fever, chills, jaundice, lethargy, and ascites. There is an acute phase of hepatocholangitis. Pruritus, which is nonspecific, eventually develops and is associated with cholestasis. The skin discoloration of jaundice occurs when bilirubin (a breakdown product of heme, mainly from myoglobin and senescent red blood cells) levels rise over 3 mg/dL.

The onset of symptoms may be delayed days to weeks after starting or discontinuing a particular drug or medication—if that is the incipient cause—and symptoms may persist for days to weeks. This form of the disease may progress to cholestasis in a minority of cases, or a mild hepatitis heralded by fever, upper abdominal pain, and dark urine, and pale stools may
occur. There may be a mild increase in aminotransfereases, alkaline phosphatase, and GGT. Eosinophilia and renal failure may occur.

**Mechanism of pathology**

Damage to the bile ducts with prolonged cholestasis, leading to the development of VBDS, may be caused by numerous entities and mechanisms\(^1\) (Table I); however, the overall pathophysiology of injury remains unknown. The underlying mechanism is believed to be similar to “immunoallergic hepatitis.” Proposed processes for bile duct loss include biliary epithelial apoptosis and necrosis\(^2\). Pathogenesis may involve the cholestatic syndromes PBC and PSC, as well as HAR, and graft-versus-host disease (GVHD). Components involved in these autoimmune- or alloimmune-mediated cholangiopathies are CD3\(^{+}\), CD4\(^{+}\), and/or CD8\(^{+}\) T-cells. Potential triggers may include cytokines, interleukins, alpha-interferon, drug-induced injury (Table II), bacterial or viral infection, or pregnancy\(^2\), which can stimulate immune cells to migrate into particular portal tracts and bile ducts (a process termed epitheliotropism)\(^2\). Other causes of VBDS include: iatrogenic, related to the interventional radiologic procedures transcatheter arterial embolization and hepatic arterial infusion chemotherapy; radiation-induced; and necrotizing arteritis, as occurs in periarteritis nodosa\(^2\).

Differential diagnosis of VBDS mainly consists of similar pathological conditions that mimic its effects and damage on the liver. These conditions include PBC, PSC, secondary biliary cirrhosis (SBC), autoimmune cholangitis, GVHD, and IAD (Table III).

Primary biliary cirrhosis involves an inflammatory reaction with progressive destruction of small intrahepatic septal and interlobular bile ducts leading to blockage. It is commonly seen in women in their 40s, and has been found to be associated with the presence of antimitochondrial antibodies (AMAs) in the blood, indicating an immune-mediated etiology. Its incidence is 5.8-15 cases per 1 million\(^3\), and it accounts for 0.6-2% of deaths due to cirrhosis worldwide. Elevated hepatic parenchymal copper levels are...
Because of blockage of the biliary ducts, bile accumulates in the liver and damages the hepatic cells. Laboratory work-up shows elevated LFTs, alkaline phosphatase, bilirubin, and calcium levels. Parenchymal copper levels are high as in PBC. Symptoms can range from a total lack thereof to generalized weakness and fatigue, pruritus, jaundice, and chronic diarrhea. Complications include cholangitis and liver failure. Mean age of diagnosis is approximately 40 years, and involves visualization of the biliary tree with an ERCP, which shows multifocal band-like strictures and dilatations of the bile ducts in a “beaded” appearance, including segmental ductal narrowing. Focal occlusion may even occur. As opposed to VBDS and PBC, histology following a biopsy may not show definitive changes in the liver in PSC. An ERCP can also be utilized in treatment by performing dilatation of the strictures. Given the circumstances, UDCA, antibiotics (for the occurrence of bacterial cholangitis), vitamin supplements, and liver transplant may be indicated. However, there is very little beneficial effect of medical therapy on overall survival. Ten percent of patients develop cholangiocarcinoma. Median time to liver transplant is about 10 years, and most outcomes are successful (> 90% at most transplant centers). Indications for transplant include refractory ascites, encephalopathy, bleeding esophageal varices, and liver failure due to cirrhosis. For both PBC and PSC, the exact cause is unknown.

Vanishing bile duct syndrome can be seen in patients who develop GVHD as well. Graft-versus-host disease occurs following allograft bone marrow transplantation or after an immunosuppressed patient receives a nonirradiated blood transfusion. An acute reaction occurs within 6 weeks and mainly affects the liver and gastrointestinal tract, with symptoms of jaundice, diarrhea, and skin rash. A chronic reaction

### TABLE III

**Differential Diagnosis of Vanishing Bile Duct Syndrome**

<table>
<thead>
<tr>
<th>Condition</th>
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<td>Viral hepatitis</td>
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<td>Alcoholic hepatitis</td>
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<td>Primary biliary cirrhosis</td>
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<tr>
<td>Primary sclerosing cholangitis</td>
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<tr>
<td>Cholestasis of pregnancy</td>
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<tr>
<td>Paraneoplastic syndrome</td>
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also found. The condition can be related to thyroid diseases, connective tissue pathology (Raynaud’s disease, scleroderma), osteoporosis, osteopenia, and osteomalacia. Signs and symptoms include loss of appetite and weight loss, xanthomas, and pruritus. Treatment includes ursodeoxycholic acid (UDCA) and liver transplant, calcium and vitamin D for metabolic bone disease, cholestyramine (a bile acid–sequestering agent), naltrexone, oxazepam, rifampin, medium-chain triglycerides for malabsorption, and dietary fat restriction. Other than a liver transplant, no medical treatment has been found to improve mortality, although symptoms and elevated aminotransferases may improve. In fact, steroids administered to reduce the inflammatory process have been found to aggravate metabolic bone disease. Diagnostic work-up typically reveals a high alkaline phosphatase and total bilirubin. An AMA titer should be checked if this diagnosis is suspected, and a liver biopsy eventually done.

The prevalence of PSC cases total 2–7 per 100,000 worldwide. It is a similar parenchymal cholestatic syndrome, with disease pathology able to randomly occur both intrahepatically (as in VBDS) and extrahepatically along the entire biliary tract, from the gallbladder to the small intestine. Investigations have found the disease to have a genetic component; many cases are related to the histocompatibility human leukocyte antigen (HLA)-B8 (seen in celiac disease) and HLA-DR3 haplotypes. It affects more men (75% of cases) than women, and 75–85% of cases have been found to be related to inflammatory bowel disease, specifically ulcerative colitis. Because of blockage of the biliary ducts, bile accumulates in the liver and damages the hepatic cells. Laboratory work-up shows elevated LFTs, alkaline phosphatase, bilirubin, and calcium levels. Parenchymal copper levels are high as in PBC. Symptoms can range from a total lack thereof to generalized weakness and fatigue, pruritus, jaundice, and chronic diarrhea. Complications include cholangitis and liver failure. Mean age of diagnosis is approximately 40 years, and involves visualization of the biliary tree with an ERCP, which shows multifocal band-like strictures and dilatations of the bile ducts in a “beaded” appearance, including segmental ductal narrowing. Focal occlusion may even occur. As opposed to VBDS and PBC, histology following a biopsy may not show definitive changes in the liver in PSC. An ERCP can also be utilized in treatment by performing dilatation of the strictures. Given the circumstances, UDCA, antibiotics (for the occurrence of bacterial cholangitis), vitamin supplements, and liver transplant may be indicated. However, there is very little beneficial effect of medical therapy on overall survival. Ten percent of patients develop cholangiocarcinoma. Median time to liver transplant is about 10 years, and most outcomes are successful (> 90% at most transplant centers). Indications for transplant include refractory ascites, encephalopathy, bleeding esophageal varices, and liver failure due to cirrhosis. For both PBC and PSC, the exact cause is unknown.

Vanishing bile duct syndrome can be seen in patients who develop GVHD as well. Graft-versus-host disease occurs following allograft bone marrow transplantation or after an immunosuppressed patient receives a nonirradiated blood transfusion. An acute reaction occurs within 6 weeks and mainly affects the liver and gastrointestinal tract, with symptoms of jaundice, diarrhea, and skin rash. A chronic reaction
develops between 100 and 400 days after the transplant and involves multiple organs, such as lacrimal and salivary glands, as well as those typically affected by the acute form. The acute form has a 50% mortality rate due to liver failure, whereas the chronic form can have a similar statistic due to secondary infections.

Autoimmune cholangitis involves intrahepatic cholangiopathy, with the occurrence of portal and periportal inflammation, intraacinar hepatitis, and piecemeal necrosis. Laboratory tests are similar to PBC, except AMA is negative while ANA is positive. Treatment involves use of prednisone. Idiopathic adulthood ductopenia is a type of VBDS in which both AMA and ANA are negative.

Secondary biliary cirrhosis occurs in patients who have extrahepatic biliary obstruction secondary to a gallstone, strictures, a tumor, or an abdominal mass or enlarged lymph node blocking the bile ducts. This can also occur in patients suffering from congenital biliary atresia. Due to the blockage and subsequent impaction of bile, the ducts and cholangiocytes are damaged, and inflammation and scarring consequently occur. Patients become jaundiced, and an ascending cholangitis due to bacteria may complicate the condition. Serum alkaline phosphatase and cholesterol levels are elevated. If the obstruction is not reversed, cirrhosis may develop over time.

Bacterial or viral infection may cause an acute ascending cholangitis or pyogenic cholangitis. This could cause the formation of a cholangitic abscess with biliary epithelial damage. If cholestasis becomes severe, symptoms similar to PBC can develop, such as hepatosplenomegaly, elevated lipids, xanthelasmas and xanthomas, and gastrointestinal malabsorption. Approximately 25% of cases develop SBC.

Vanishing bile duct syndrome follows extensive and irreversible ductopenia, which is the obliteration of interlobular and septal bile ducts with replacement by a richly elastic fibrous core. It is a heterogeneous clinicopathologic entity that eventually leads to progressive cholestasis, portal inflammation, fibrosis of the biliary tree, end-stage liver disease, cirrhosis, and liver failure. Patients with prolonged VBDS may have copper granule deposition and Mallory body formation. The few lymphocytes present are Leu 4+ and Leu 2a suppressor/cytotoxic T-cells. The mechanism of loss is twofold: T-cell–mediated (more likely to be reversible) and ischemic sequelae caused by obliterator arteriopathy. Vanishing bile duct syndrome also occurs in approximately 10% of liver transplant patients within a 100-day period of the procedure. Given that only a minority of exposed patients develop immunization and hepatocholangitis, it is believed that a genetic predisposition may be involved. The syndrome can also occur in rare congenital cases (eg, Alagille syndrome, cystic fibrosis, duct plate abnormalities), malignancy (eg, cholangiocarcinoma, histiocytosis X, Hodgkin’s lymphoma, mastocytosis), infections (eg, CMV, reovirus, parasites, recurrent biliary sepsis), HAR, IAD, ischemic episodes (eg, hepatic artery thrombosis, surgical causes, vasculitis), sarcoidosis, after high-dose chemotherapy and autologous peripheral stem cell transplantation, and in patients taking certain drugs such as chlorpromazine and amoxicillin/clavulanic acid (Table II).

Damage to the interlobular bile ducts in the congenital (Alagille syndrome) or acquired form is the most common cause for chronic cholestasis in adults. There are two general presenting patterns of VBDS:

- Type 1—Patients who are asymptomatic or present only with cholestasis. They have less bile duct destruction on liver biopsy, and their clinical course ranges from spontaneous improvement to the development of biliary cirrhosis.
• Type 2—Patients presenting with decompensated biliary cirrhosis and who have marked destruction of intrahepatic bile ducts and require orthotopic liver transplantation (OLT), which will completely resolve the jaundice and pruritus. Treatment depends on the cause, but most instances are treated with hydrophilic bile acid (BA) UDCA.

Treatment

Treatment of VBDS has been limited to alleviating symptoms. Medications such as steroids have been ineffective. Use of UDCA, which may be used to dissolve gallstones, has been shown to be effective specifically in one case of VBDS related to prochlorperazine and in one related to chlorpromazine, but the results are controversial. Ursodeoxycholic acid acts by several mechanisms to improve bile flow and liver function in intrahepatic cholestasis. It displaces the more hydrophobic BAs at the terminal ileum from re-uptake into the enterohepatic circulation, and likely within the liver cell as well, thus reducing membrane damage, stimulating the secretion of the hydrophobic BA and phospholipids (thereby reducing the overall hydrophobicity of the retained bile) and possibly stimulating cholangiolar bile secretion. Ursodeoxycholic acid may also minimize the immune response by reducing HLA expression on hepatocytes and bile duct epithelium. Use of endoscopic interventions (ie, balloon dilation) may also be used to treat this condition.

Orthotopic liver transplantation is the standard intervention for SBC and hepatic failure. In most cases, symptomatic manifestations show complete resolution. However, if the disease occurs after a liver transplant, because the lesion is usually irreversible, treatment often requires retransplantation. In general, a liver transplant should be considered for any patient with end-stage acute or chronic hepatic disease, aspects of which may include the following refractory symptoms: pruritus, ascites, portal systemic encephalopathy, severe fatigue, hepatorenal syndrome, and abnormal laboratory work such as bilirubin greater than 10 mg/dL, albumin less than 2.5 g/dL, and an international normalized ratio greater than 2. An OLT can be done in a patient who has a history of alcoholism if the patient has refrained from alcohol use for at least 6 months. Liver function tests slowly improve over months to years with response to treatment.

OUTCOME OF THE CASE PATIENT

After diagnosis of VBDS, a conservative approach was agreed on, and the patient was closely followed at regular intervals by the outpatient hepatology service. If symptoms and hepatic function worsened significantly, a liver transplant would be the next option.

The patient’s numerous diagnostic evaluations and work-up were appropriate. An abdominal ultrasound is a simple and noninvasive technique to view the biliary tract and assess for the presence of gallstones, although it may miss 25–40% of such stones, depending on operator expertise and interfering inflammation or fatty tissue of the patient. A CT scan may determine the presence or absence of dilated bile ducts and/or an obstruction. Helical CT scans have increased the sensitivity for detecting stones in the bile duct. Like ultrasound, a CT may not detect duct pathology if an acute obstruction is occurring, such as a duct taking a week to dilate after a gallstone becomes impacted.

Both ERCP (which is invasive, using injected radiopaque contrast that is monitored under fluoroscopic guidance) and MRCP (noninvasive, utilizing T2-weighted imaging) will provide an anatomical
outline to help visualize the pancreatic and biliary ductal tree, thereby determining the presence and degree of stones, strictures, and stenosis.

It should be noted that an infection, such as in the urinary tract or a pneumonia, as well as dehydration, are common causes of delirium and altered mental status in the elderly population, as was seen in this patient.

The author reports no relevant financial relationships.

REFERENCES