Caroli Disease Presenting with Atypical Chest Pain

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INTRODUCTION

Caroli Disease (CD) was first described by Dr. Jacques Caroli in 1958 as cystic dilatation of the intrahepatic bile ducts without other apparent hepatic abnormalities.[1] The incidence is approximately 1 in 1,000,000.[2] This cystic dilation affects the entire liver or parts of it, and nonobstructive saccular or fusiform dilatation of the intrahepatic bile ducts is seen. The dilatation is usually segmental or saccular and associated with stone formation, which leads to recurrent bacterial cholangitis.[3] This is usually referred to as the pure form, which occurs only in about 15% of cases.[4] The second form is associated with portal hypertension and eventual liver failure as a result of subsequent hepatic fibrosis.[5] Both forms can be seen at an early age and even as late as the fifth decade of life.[6] CD can also be associated with cystic diseases of the pancreas, cystic disease of the kidney, most notably renal tubular ectasia, choledochal cysts, and cholangiocarcinoma.[7]

Caroli Syndrome (CS), a form of CD that presents with congenital hepatic fibrosis, is linked to pathogenic mutations in the PKHD1 gene, which cause autosomal recessive polycystic kidney disease (ARPKD). The polycystic kidney and hepatic disease 1 (PKHD1) gene produce fibrocystin, a large integral membrane protein found on chromosome 6 (6p21-p12).[8] This protein has structural similarities to the hepatocyte growth factor receptor and appears to be a member of a protein superfamily that regulates cell proliferation, differentiation, cell adhesion, tubulogenesis, cell polarity, and cell-matrix interactions.[9-10] PKHD1 is largely expressed in the kidneys, with lesser amounts in the liver, pancreas, and lungs, a pattern that matches the disease's phenotype, which primarily affects the liver and kidneys.

To date, the molecular pathophysiology of CD is still unknown. The pathophysiology of CS is thought to be secondary to intrahepatic ductal dilatation and hepatic fibrosis linked to a halt or disruption in the development of the ductal plate of the larger intrahepatic bile ducts.[11] A genetically regulated failure of cholangiocyte homeostasis enhances the release of chemokines that attract macrophages and orchestrate a pro-fibrotic tissue response in congenital hepatic fibrosis.[12]

CD is typically diagnosed incidentally on imaging after seemingly-typical presentations of cholangitis or abdominal pain with elevated liver enzymes are investigated further.

CASE PRESENTATION

A 43 year old female with past medical history of fibromyalgia, anxiety, and depression presented to the emergency department with a three day history of diffuse abdominal pain, nausea, vomiting, and substernal chest pain. She denied experiencing symptoms like these before. Chest pain was atypical in nature, and workup including ECG and troponin were negative for signs of cardiac ischemia. Due to recent tubal ligation surgery, transvaginal ultrasound was performed, but only revealed multiple nabothian cysts on the cervix. CT Abdomen/Pelvis with contrast was then performed, which revealed innumerable cystic lesions clustered about the porta hepatis; choledocholithiasis could not be excluded; cholelithiasis was also seen. Notable lab values included AST 136 and ALT 251, which were within normal limits when checked one month prior. Patient was discharged from the ED and instructed to follow up with her Primary Care Physician (PCP). She was seen in the clinic 4 days later, at which time an MRCP was ordered to rule out choledocholithiasis. The MRCP revealed cystic lesions within the liver around the porta hepatis and following the most inferior left-sided and right-sided biliary radicals; multiple stones were also seen in the gallbladder. The findings were thought to be manifestations of CD. At her subsequent follow up appointment with PCP, she continued to complain of diffuse relapsing and remitting abdominal pain without any specific provoking factors. A CMP was drawn which revealed downtrending of liver enzymes with AST 33 and ALT 58. She was referred to a local gastroenterologist where bidirectional endoscopy was planned. The patient was thereafter recommended to follow up with a GI clinic at a tertiary center specializing in Caroli disease.

IMAGING

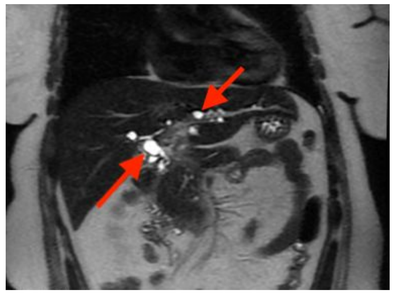

Figure 1. MRCP Coronal View
Red arrows demonstrate cystic lesions around porta hepatis

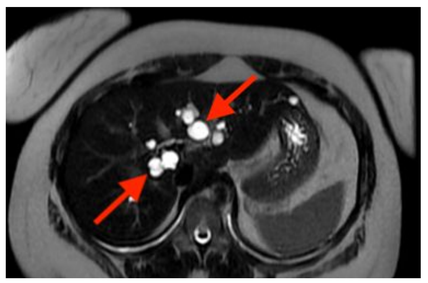

Figure 2. MRCP Axial View
Red arrows demonstrate cystic lesions around porta hepatis

DISCUSSION

Patients with CD present with a wide variety of symptoms. Most patients initially present with abdominal pain, pruritus, hepatomegaly and other sequelae secondary to biliary abnormalities and portal hypertension. Complications of CD include acute bacterial cholangitis with septicemia and abscess formation. These have been thought to be secondary to the biliary stasis seen in CD.[11]

CD can be diagnosed via a myriad of imaging modalities including ultrasound, CT, and MRCP.[12] Imaging studies usually demonstrate cystic dilation of intrahepatic ducts in the proximal region, bile duct ectasia and normal common bile duct.[13] CT or MRCP can demonstrate intense enhancement within dilated ducts that is pathognomonic for CD and is also known as the central dot sign.[14] Liver biopsy isn't necessary for diagnosis, but when performed, pathology will show bands of mature, fibrotic tissue, potentially hypoplastic portal vein branches and possible inflammatory cells surrounding bile ducts.[15]

Management varies based on complications patients present with and should be individualized because of numerous different presentations. Patients should be referred to a gastroenterologist in order to have EGD performed for variceal screening. Patients with esophageal varices should be started on non-selective beta blockers.[16] New diagnosis of stricture or decompensation of condition without any other explainable cause should raise suspicion for cholangiocarcinoma and should possibly undergo CA19-9 surveillance assays.[17] Patients that develop chronic cholestasis due to this disease process should be started on fat soluble vitamin supplementation.[18]

For those that present with acute cholangitis should be treated with antibiotics and be considered for ERCP performed to treat possible choledocholithitiasis. Cholangitis as a complication of CD is especially difficult to treat and may require antibiotics for longer durations than patients that present with typical cholangitis, due in part to inherent bile stasis involved in the disease process.[19]

Stone extraction management is dictated based on the location of the stone. Common bile duct stones can be simply managed via sphincterotomy and stone removal endoscopically, whereas intrahepatic stones may require intraductal electrohydraulic lithotripsy, extracorporeal shock wave lithotripsy, or oral cholangioscopy removal.[20-21]

For patients that cannot undergo endoscopy, or lithotripsy, synthetic bile salts like ursodeoxycholic acid (UDCA) can partially or completely dissolve stones, via increased bile flow. The recommended dose of UDCA is 10 to 20 mg/kg per day.[1]

Prognosis of CD varies greatly based on complications. Recurrent cholangitis and stones often require liver transplantation. Recurrent inflammation from infections have also rarely caused amyloidosis.26 Due to bile stasis, cholangiocarcinoma related to CD has risk as high as 7%.[22]

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