CLINICAL VIGNETTE

Asymptomatic Presentation of Intrahepatic Cholangiocarcinoma

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Presentation

A 66-year-old male presented for evaluation of elevated alkaline phosphatase of 202 U/L. His past medical history includes type II diabetes, gout, alkaline phosphatase the year prior was normal. Gamma-glutamyl transferase (GGT) was elevated at 386 U/L and the remainder of his liver function tests including total bilirubin, albumin, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were normal. The patient denied fatigue, nausea, vomiting or abdominal pain. He reported no change in appetite or bowel habits or weight loss. On physical exam, he had no jaundice, hepatomegaly, right upper quadrant mass or pain. Ultrasound showed new left intrahepatic biliary dilatation to 6 mm. No sonographic mass was visualized. Magnetic resonance cholangiopancreatography (MRCP) showed left-sided intrahepatic biliary dilatation with irregular enhancement of the common bile duct and left hepatic duct. Positron emission tomography (PET) showed no areas of uptake. Cancer antigen 19-9 (CA 19-9) was elevated at 35 units/ milliliter and carcinoembryonic antigen (CEA) was normal.

During his evaluation for cholangiocarcinoma, he presented to the emergency room with leg swelling and shortness of breath and was found to have decompensated heart failure. He was admitted, diuresed and started on guideline-directed medical therapy. Coronary angiogram was negative for obstructive coronary artery disease and had non-ischemic heart failure with an ejection fraction of 25%. After discharge, endoscopic retrograde cholangiopancreatography (ERCP) showed a 3.5 cm stricture of the common bile duct that was stented and biopsied. The biopsy showed moderately differentiated adenocarcinoma. Based upon the location in the gallbladder, the patient was diagnosed with intrahepatic cholangiocarcinoma. The day after his ERCP, he developed severe right upper quadrant abdominal pain with elevated lipase, consistent with post-ERCP pancreatitis and was re-admitted. During hospitalization, he developed ascites with paracentesis negative for malignancy. His hospitalization was complicated by acute kidney injury and enterococcus urinary tract infection. Repeat abdominal showed peritoneal nodularity concerning for peritoneal carcinomatosis. The patient was offered and declined palliative chemotherapy and was discharged on hospice care.

Discussion

Cholangiocarcinoma is an uncommon and aggressive malignancy. Cholangiocarcinoma is divided into intrahepatic, perihilar and extrahepatic subtypes based upon location.

Perihilar cholangiocarcinoma accounts for the majority of cholangiocarcinoma cases (50%).[1] Extrahepatic cholangiocarcinoma constitutes 40% of cases, and intrahepatic 10%.[1] Intrahepatic cholangiocarcinoma is an incidental diagnosis in 19-43% of cases.[2] This malignancy is the second most common primary hepatic tumor and represents 3% of all gastrointestinal cancers.[3] The average age at presentation is 70 years with a male predominance of 1.5:1.[4] The incidence is high in Southeast Asia with an annual incidence of 71.3/100,000 cases as compared with Europe at 1.8/100,000 and the United States of America at 1/100,000.[2]

Risk factors for cholangiocarcinoma include primary sclerosing cholangitis, parasitic infections, hepatolithiasis and viral hepatitis/cirrhosis. Primary sclerosing cholangitis (PSC) is a well-known risk factor for cholangiocarcinoma, commonly affecting individuals within two years after the diagnosis of PSC.[1] Parasitic infections common in Southeast Asia like *Opisthorchis viverrini* and *Clonorchis sinensis* increase the risk of cholangiocarcinoma in affected individuals. Hepatolithiasis is common in Korea and Japan, and endemic in China. Up to 10% of patients with hepatolithiasis will develop cholangiocarcinoma.[4] The stones are thought to increase risk of malignancy by producing bile stasis and cholangitis.[4] Hepatitis B and C are also risk factors for cholangiocarcinoma.

The clinical presentation differs between intrahepatic (ICC) and extrahepatic cholangiocarcinoma (ECC). ECC causes biliary obstruction, so it commonly presents with painless jaundice, pruritis, pale stools and dark urine. However, ICC is typically asymptomatic and commonly is found due to abnormal labs or imaging. If ICC does cause symptoms, they include weakness, fatigue, weight loss, and right upper quadrant abdominal pain. Physical exam may demonstrate jaundice, hepatomegaly or a mass in the right upper quadrant. The finding of a palpable gallbladder is rare. Skin findings associated with cholangiocarcinoma include paraneoplastic syndromes like erythema multiforme, Sweet syndrome or acanthosis nigrans.

Commonly used diagnostic tests including imaging and tumor markers. Ultrasound with ICC can demonstrate dilated intrahepatic ducts. Distal ECC can have dilated intra and extrahepatic ducts. The National Comprehensive Cancer Center recommends triple phase CT or MRCP for diagnosis of suspected cholangiocarcinoma.[4] ERCP can identify the location of the stricture and biopsy the lesion. Obtaining a pathologic

diagnosis can be challenging in cholangiocarcinoma. PET imaging can be used to diagnose cholangiocarcinoma with 60-92% sensitivity and 93% specificity.[2] PET is most helpful in detecting distant metastases. MRI can differentiate between cholangiocarcinoma and hepatocellular carcinoma (HCC). While HCC shows enhancement in the arterial phase with venous washout, cholangiocarcinoma will show uptake in arterial and venous phases. MRI may show rim enhancement in cholangiocarcinoma as the tumor is highly vascularized and has increased uptake at the edges.[1] Labs including LFTS are important to obtain as well as tumor markers like CA 19-9. There are no specific tumor markers for cholangiocarcinoma, but CA 19-9 may be elevated. In patients with PSC with intrahepatic cholangiocarcinoma, CA 19-9 values over 129 U/ml have sensitivity of 79% and a specificity of 98%. A CA 19-9 level over 1,000 U/ml is concerning for metastasis to the peritoneum.[1] Staging of intrahepatic cholangiocarcinoma is done according to the 7th edition of American Joint Committee on Cancer TNM staging for intrahepatic cholangiocarcinoma.[4]

The treatment for cholangiocarcinoma is surgery with negative margins. Median survival with patients who have resectable disease is 36 months.[1] Most patients are not surgically resectable at diagnosis. Intrahepatic cholangiocarcinoma frequently metastasizes through the lymphatic system or biliary tree. For patients who do have resection, recurrence is common. Palliative options include chemotherapy with gemcitabine and cisplatin and radiotherapy.[4]

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