CLINICAL VIGNETTE

Cholangiocarcinoma in a 28-Year-Old Female

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Case Presentation

A 28-year-old female with no significant medical history presents with intermittent cramping right-sided abdominal and flank pain over six weeks. The pain worsens with laughing and can limit her ability to take a deep breath. She initially attributed the pain to stress and has some pain free days. There is no associated fever, nausea, jaundice, or changes in urine or stool. There is no pain associated with eating, but she has lost 20 pounds intentionally over the last year.

There is no pertinent family or past medical history. Her only medication is NuvaRing for the past five years. She drinks one glass of wine with dinner several nights per week. There is no history of tobacco or drug use, tattoos or transfusions. She takes no herbs or supplements and had no significant travel for 6 months prior to symptom onset.

On exam, vital signs were all within normal range, with blood pressure of 101/69 mmHg, heart rate of 74 beats per minute, temperature of 36.6 degrees Celsius and a body mass index of 26.9 kg/m^2. Her abdominal examination was notable for mild tenderness to palpation in the right upper quadrant without rebound or guarding and negative Murphy's sign. The liver edge was palpable approximately 2 cm below the costal margin.

Labs and abdominal ultrasound were ordered. White blood cell count was 6.7, hemoglobin 12.6 and platelets 305. Chemistries included normal aspartate aminotransferase (AST) of 25, alanine aminotransferase (ALT) of 17, and normally elevated alkaline phosphatase of 117 (normal < 113), with total bilirubin of 0.3.

Abdominal ultrasound showed a diffusely heterogeneous liver with multiple indeterminate ill-defined hypoechoic regions. Magnetic resonance imaging (MRI) showed multiple hypo-enhancing masses occupying most of the posterior right hepatic lobe, worrisome for either primary hepatic malignancy or metastatic disease. There was also periportal and upper retro-peritoneal lymphadenopathy and a thrombosed posterior branch of the right portal vein.

Computed tomography (CT)-guided liver biopsy revealed adenocarcinoma of pancreatobiliary origin. Staging CT con-firmed the liver masses as well as retroperitoneal, abdominal and mediastinal lymphadenopathy.

Additional labs included normal alpha fetoprotein (AFP) of 5.1, carbohydrate antigen 19-9 (CA 19-9) of 6 and carcino-embryonic antigen (CEA) of 2.3. Gamma-glutamyltransferase (GGT) was mildly elevated at 83 (normal < 68). Hepatitis serolo-gies confirmed prior hepatitis A and B vaccination and no hepatitis C.

She was treated for multifocal intrahepatic cholangiocarcino-ma. Initial treatment included chemotherapy with gemcitabine and cisplatin, followed by right hepatic lobectomy and addi-tional cycles of gemcitabine and cisplatin.

Discussion

Cholangiocarcinoma arises from epithelial cells within the biliary tree. Anatomically, it is classified as intrahepatic, peri-hilar (Klatskin tumor), or extrahepatic (distal).[1,2] Intrahepatic cholangiocarcinoma is proximal to the second degree bile ducts and comprises less than 10% of cases. Perihilar cases have involvement between the second degree bile ducts and where the cystic duct joins the common bile duct. These represent 50% of patients. Extrahepatic cholangiocarcinoma is distal to the confluence and the ampulla of Vater and makes up the remaining 40%.[1] A rare mixed hepatocellular-cholangiocellular carcinoma was recently classified as a distinct subtype but only comprises <1% of liver malignancies.[3]

Cholangiocarcinoma has higher incidence in Hispanic and Asian populations. There is also a slight male predominance. Patients with primary sclerosing cholangitis (PSC) have mean age at diagnosis in the 30s versus 60s in those without PSC.[4-6]

Primary sclerosing cholangitis is a well-known risk factor for cholangiocarcinoma, with lifetime incidence up to around 10%.[7,8] Other risk factors include cirrhosis, hepatitis B and C, bile duct cystic disorders, Caroli's disease, hepatolithiasis, hepatobiliary flukes, and toxins. Hepatobiliary flukes (*Opisthorchis viverrini* and *Clonorchis sinensis*) and hepato-lithiasis are more common in Southeast Asia. However, most cases have no identifiable risk factor.[3,4]

Patients with cholangiocarcinoma present with painless jaundice (particularly with extrahepatic cholangiocarcinoma), abdominal pain, weight loss, nausea and poor appetite.[2,9]

Intrahepatic cholangiocarcinoma typically presents as a mass in a non-cirrhotic liver. Thus, it needs to be differentiated from hepatocellular carcinoma. Imaging can often differentiate between the two. Mixed hepatocellular-cholangiocellular carcinoma can complicate the diagnosis though some cases may be differentiated by imaging. Biopsy can establish diagnosis for intrahepatic lesions.[9] Endoscopic ultrasonography (EUS) may also help diagnosis by providing additional information regarding vascular involvement, size, location and lymph node involvement. Tumor sampling is not recommended for perihilar lesions, as seeding may preclude curative treatment.[9]

Carbohydrate antigen 19-9 (CA 19-9) is a biomarker for cholangiocarcinoma, although elevation does not necessarily indicate malignancy.[9]

Surgery is the preferred treatment, however only 25-30% present with resectable disease.[2] Liver transplant is a rare option in very select cases. Other surgical factors include vascular and lymphatic involvement and presence of metastatic disease.[9] Due to high recurrence rates, adjuvant chemotherapy (such as with gemcitabine and cisplatin) is often used. In patients with unresectable or recurrent disease, first line chemotherapy is typically gemcitabine and cisplatin.[2,10] Immunotherapy and molecularly targeted therapies are being studied as well with pemigatinib and futibatinib (inhibitors of fibroblast growth factor receptor [FGFR]) as newer treatment options.[2] Endoscopic retrograde cholangiography with cytology brushing can assist evaluation and potential therapy with stent placement.[9]

Cholangiocarcinoma is an aggressive bile duct malignancy which can present in younger patients with evolving treatment options.

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