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CLINICAL VIGNETTE

A 67-Year Old Male with Obstructive Jaundice

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Case Report

A 67-year-old war veteran male presented for evaluation of jaundice. The patient reported anorexia with increasing nausea and vomiting for 2 to 3 days. He noted fatigue, diffuse pruritus and jaundice with "coca-cola" colored urine. He denied fevers, sweats, and hematemesis, but had noticed some abdominal distension. He had no history of hepatitis, intravenous drug abuse (IVDA) or significant alcohol or acetaminophen use. Patient was a retired commercial building painter. He denied recreational or occupational exposure to hepatotoxic chemicals except for paint. He was physically active, riding his bicycle up to 100 miles per day. His only medicine was ibuprofen taken for knee pain.

On physical examinations, the patient was pleasant, and appeared in no distress except for occasional scratching. He was afebrile with blood pressure of 128/73 mm Hg, and heart rate of 95 beats/min. He was deeply jaundiced. Abdominal examination revealed tenderness to palpation of epigastrium, right upper quadrant and bilateral lower quadrants with no rebound or guarding. He was alert and oriented without asterixis.

Labs were remarkable for Alb: 2.6 g/dL, AST: 191 U/L ALT: 187 U/L Alk Phos: 853 U/L TBili: 22.5 mg/dL DBili: 5.7 mg/dL, CA 19-9 was high at 83 U/ml, CEA was within normal limits. Abdominal ultrasound showed intrahepatic bile duct dilatation, mildly contracted gallbladder with wall thickening, and a complex cystic lesion within the body of the pancreas. Abdominal CT (**Figure 1**) revealed common hepatic duct wall thickening and enhancement with intrahepatic biliary dilatation, highly suspicious for cholangiocarcinoma as well as cardiophrenic, celiac, gastrohepatic, portacaval, porta

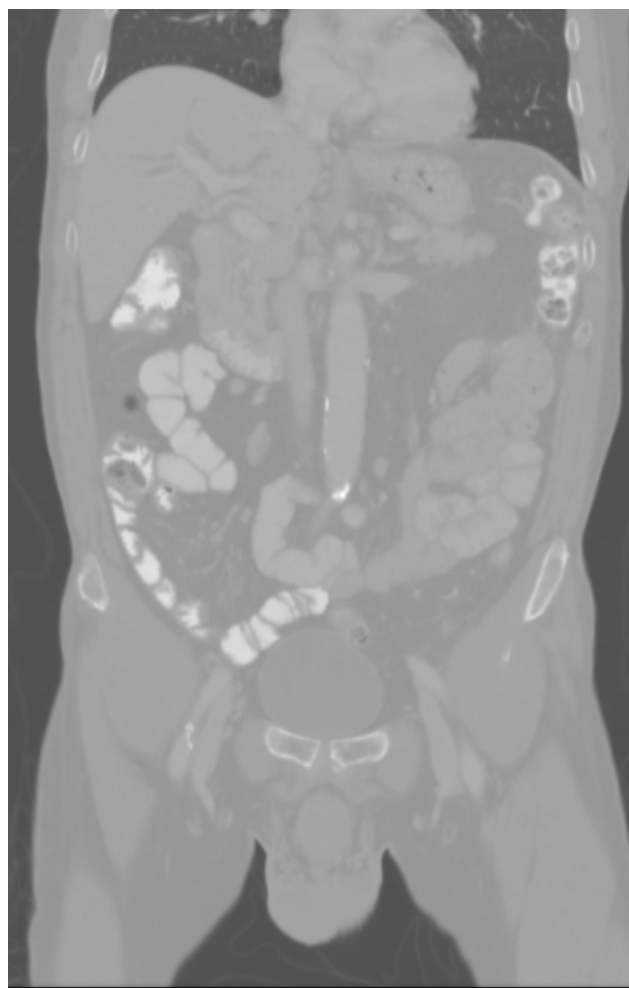


Figure 1: Abdominal CT

hepatic and mesenteric lymphadenopathy. The patient decompensated rapidly despite Endoscopic retrograde cholangiopancreatography (ERCP), broad spectrum antibiotics, biliary drainage and stent placement with complications of sepsis, hepatorenal syndrome requiring dialysis, and disseminated intravascular coagulopathy. He died 1 month following admission, but postmortem examination failed to identify cholangiocarcinoma.

History of Cholangiocarcinoma

Cholangiocellular carcinoma (CLC) is an uncommon liver tumor which was first defined by Steiner, et al. in 1957¹. CLC is thought to be derived from Hering's canal because tumor glands of CLC are morphologically similar to cholangioles¹. It is a primary adenocarcinoma that arises from a bile duct, and is second in frequency after hepatocellular adenoma of the liver. It is associated with inflammatory disorders and

malformations of the ducts, but most cases are of unknown etiology. Cholangiocarcinoma resembles adenocarcinomas arising in other tissues, so a definitive diagnosis relies on the exclusion of an extrahepatic primary and distinction from benign biliary lesions². The incidence of bile duct cancer is low but increasing. Determinants of survival vary in the literature, due to a lack of sufficient numbers of patients in most series³. Cholangiocarcinomas account for approximately 3% of all gastrointestinal malignancies, with a prevalence in autopsy studies of 0.01% to 0.46%. The reported incidence in the United States is 1 or 2 cases per 100,000 population. About 8,500 cases of extrahepatic bile duct cancer are diagnosed annually in the United States, two-thirds of which are gallbladder cancers. The balance, approximately 2,000 to 3,000 cases per year, are extrahepatic cholangiocarcinomas.

For unclear reasons, the incidence of intrahepatic cholangiocarcinoma has been rising over the past 2 decades in Europe (but not Denmark⁵), North America, Asia, Japan, and Australia, while rates of extrahepatic cholangiocarcinoma are declining internationally⁶.

The incidence of biliary tract cancers increases with age; the typical patient with cholangiocarcinoma is between 50 and 70 years of age. However, patients with primary sclerosing cholangitis (PSC) and those with choledochal cysts present nearly 2 decades earlier⁴. In contrast to gallbladder cancer, where female gender predominates, the incidence of cholangiocarcinoma is slightly higher in men. This probably reflects the higher incidence of PSC in men⁷.

Many risk factors have been identified. In the United States and Europe, the main risk factors are PSC and choledochal cysts. Other risk factors are fibropolycystic liver disease (congenital anomalies like Caroli's), parasitic infection (in Asia and Thailand, liver flukes of the genera *Clonorchis* and *Opisthorchis*), Cholelithiasis and Hepatolithiasis, toxic exposures (a clear association exists between exposure to the radiologic contrast agent Thorotrast [a radiologic contrast agent banned in the 1960s for its carcinogenic properties] and subsequent cholangiocarcinoma, malignancy usually develops 30 to 35 years after exposure)⁸, Lynch syndrome and biliary papillomatosis (two genetic disorders)⁹, non viral

chronic liver disease, HIV, Diabetes, viral liver disease, and obesity.

The differential diagnoses of cholangiocarcinoma are the same as for any obstructive jaundice, and include choledocholithiasis, benign bile duct strictures (usually postoperative), sclerosing cholangitis, or compression of the common bile duct by either chronic pancreatitis or pancreatic cancer.

Cholangiocarcinomas usually become symptomatic when the tumor obstructs the biliary drainage system, causing painless jaundice. Common symptoms include pruritus (66%), abdominal pain (30% to 50%), weight loss (30% to 50%), and fever (up to 20%)¹⁰. Symptoms related to biliary obstruction include clay-colored stools and dark urine.

Diagnosis of Cholangiocarcinoma

Diagnosis of a cholangiocarcinoma can be challenging, particularly in patients with Primary Sclerosing Cholangitis (PSC). In such cases, mass lesions are infrequently identified on imaging, and patients often do not develop significant intrahepatic biliary dilatation. A high index of suspicion, and multidisciplinary investigative procedures are needed¹¹. For the patient in this case, he had no prior history of PSC, had elevated liver function tests and his clinical picture indicated obstructive jaundice. Tumor markers and radiological tests were performed; these, however, did not make the diagnosis.

Treatment

The overall prognosis for cholangiocarcinoma is poor. The treatment necessitates a multidisciplinary approach.

Radical resection of the extrahepatic bile ducts, usually in combination with concomitant partial liver resection, remains the only curative treatment.

Liver transplantation in combination with neoadjuvant chemoradiation therapy seems to be promising in a highly selected group of patients. Palliative treatment should be targeted at adequate biliary drainage, preferably by stenting. Radiotherapy and systemic chemotherapy are not standard treatment and should be applied in an experimental setting only. New options such as photodynamic therapy and tyrosine kinase inhibitors are promising, but still experimental

treatments¹².

Surgical Treatment

"The median survivals for R0-resected intrahepatic, perihilar, and distal tumors were 80, 30, and 25 months, respectively, and the 5-year survivals were 63%, 30%, and 27%, respectively⁷³. Resection offers the best opportunity for long-term survival but is only possible in the minority, and patients with large, node-positive or multifocal IHC seem to derive little benefit. Establishing and maintaining control of the intrahepatic disease remains the biggest problem for all IHC patients. The recent increase in survival seems largely because of improved non operative therapy for unresectable disease¹³.

Discussion of Primary Sclerosing Cholangitis

Primary sclerosing cholangitis is a chronic cholestatic liver disease characterized by induration caused by obliterative fibrosis and inflammation of bile ducts resulting in strictures and destruction of the biliary tree¹⁴. It ultimately can lead to cirrhosis, end-stage liver disease, and the need for liver transplantation. The majority of cases occur in association with inflammatory bowel disease (IBD), which generally precedes the development of PSC¹⁵. It affects up to 5% of patients with ulcerative colitis, with a slightly lower prevalence (up to 3.6%) in Crohn's disease. The strength of this association means that the vast majority (> 90%) of patients with PSC also have IBD, although many may have only mild gastro-intestinal symptoms. Usually IBD presents before PSC, although the contrary can occur and the onset of both conditions can be separated in some cases by many years¹⁶. Our patient fell into this category, as he seemed healthy with no gastrointestinal complaints prior to the onset of jaundice. The etiology of PSC is unknown, there is, however, an increasing body of evidence that points to an immunologic disturbance as a component of the disease.

PSC can affect both large and small bile ducts and is also associated with a 10% to 20% lifetime risk for the development of cholangiocarcinoma, and 70% of patients with PSC will have concomitant ulcerative colitis¹⁷. PSC typically presents in the fourth or fifth decade of life, more commonly in whites and Northern European men than women¹⁸. Patients often have abnormal liver biochemistries or symptoms typical of PSC such as fatigue, pruritus, or

jaundice. The diagnosis is then confirmed by imaging studies that show diffuse beading of the bile ducts in large-duct PSC, or by histology and biochemical studies that reveal typical features of PSC with a normal cholangiogram in small-duct PSC¹⁹. Our patient, however, was in his sixth decade of life, had biochemistry and symptoms as any obstructive jaundice, so diagnosis could not be confirmed with imaging or 2 nondiagnostic biopsy attempts, delaying confirmation of diagnosis to his postmortem exam.

Risk Factors

PSC is far more common in men with 70% of all PSC patients being male. This male preponderance is absent in PSC patients without associated IBD, being equally common in both males and females²⁰. Family history of the disease has also been found to be a risk factor. There is a 0.7% risk in first-degree relatives of patients with PSC rising to 1.5% in siblings of affected individuals²¹. Our patient had a sister that died of cirrhosis of unknown etiology but no reported family history of PSC. Smoking is a well-recognized protective factor against the development of ulcerative colitis, and three studies have suggested that cigarette smoking may also additionally protect against the development of PSC²²⁻²⁴. Our patient was a non-smoker.

Treatment

There is no definitive treatment for PSC. Most treatment is geared towards prevention of progression to end-stage liver disease and CLC. Ursodeoxycholic acid (UDCA) is the only drug which has been demonstrated to have a positive effect. Some, but not all, patients show improvements in biochemistry, symptoms and histology²⁵⁻³⁰. Long-term UDCA use at high dose, 20-30 mg/kg per day (in divided doses), is the most promising new addition in treatment of PSC as this may increase clinical benefit and decrease histological progression of disease³¹⁻³². Liver transplantation is an acceptable treatment option for these patients but note that there is a 10% recurrence rate of PSC after transplantation³³.

Prognosis

PSC is generally progressive and has a poor prognosis. Median survival without liver transplantation after diagnosis is approximately 12 years³⁴ with survival worse for those who are symptomatic at presentation³⁵. Reports from single centers performing

liver transplantation in PSC patients have demonstrated excellent survival rates of 90% to 97% at one year, and 83% to 88% at 5 years^{36,37}.

The major cause of mortality is the occurrence of cholangiocarcinoma, which is significantly increased in patients with PSC who display a 10% to 15% lifetime risk of developing the disease. This risk is higher in patients with associated inflammatory bowel disease than those with PSC alone, with an estimated annual incidence of 0.5% to 1%³⁸⁻⁴⁰. Other complications of PSC are osteoporosis, gallbladder stones and polyps, peristomal varices, dominant stricture, bacterial cholangitis, gallbladder neoplasm, colonic dysplasias and neoplasm and hepatocellular cancer⁴¹.

Conclusion

Given the detailed review of both cholangiocarcinoma and primary sclerosing cholangitis, the difficulty in differentiating between the two, especially without a diagnostic biopsy, still remains.

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