CLINICAL VIGNETTE

A 67-Year Old Male with Obstructive Jaundice

Ifeoma S. Izuchukwu, M.D.

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 hepatic and mesenteric lymphadenopathy.

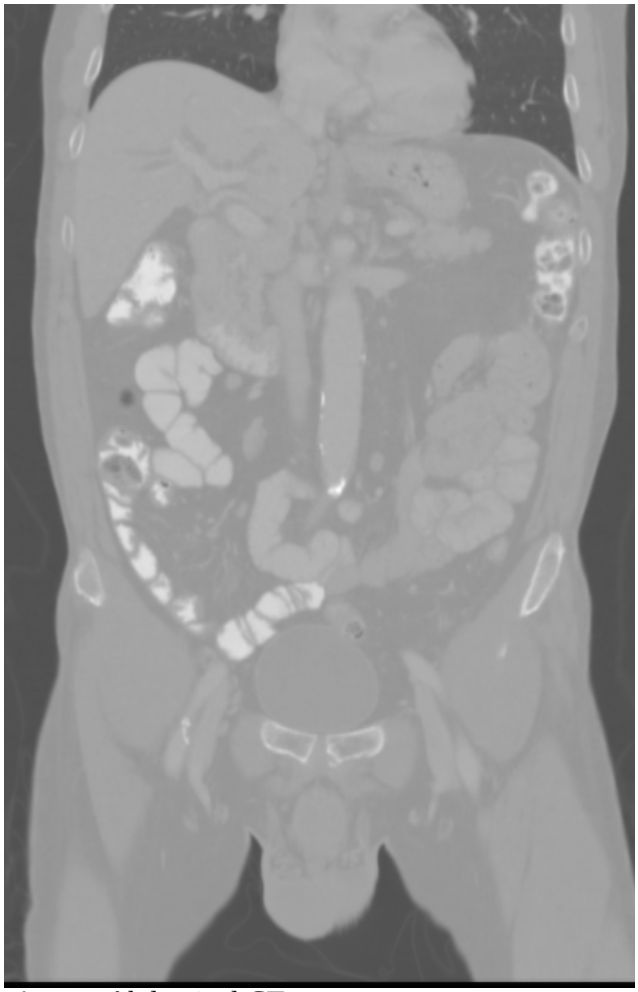

Figure 1: Abdominal CT

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 1957[1]. CLC is thought to be derived from Hering's canal because tumor glands of CLC are morphologically similar to cholangioles[1]. 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 lesions[2]. 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 series[3]. 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 Denmark[5]), North America, Asia, Japan, and Australia, while rates of extrahepatic cholangiocarcinoma are declining internationally[6].

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 earlier[4]. 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 men[7].

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 needed[11]. 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

treatments[12].

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%, respectively'[3]. 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 disease[13].

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 tree[14]. 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 PSC[15]. 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 years[16]. 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 colitis[17]. PSC typically presents in the fourth or fifth decade of life, more commonly in whites and Northern European men than women[18]. 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 PSC[19]. 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 females[20]. 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 individuals[21]. 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 PSC[22-24]. 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 histology[25-30]. 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 disease[31-32]. Liver transplantation is an acceptable treatment option for these patients but note that there is a 10% recurrence rate of PSC after transplantation[33].

Prognosis

PSC is generally progressive and has a poor prognosis. Median survival without liver transplantation after diagnosis is approximately 12 years[34] with survival worse for those who are symptomatic at presentation[35]. 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 cancer[41].

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.

REFERENCES

1. **Kanamoto M, Yoshizumi T, Ikegami T, Imura S, Morine Y, Ikemoto T, Sano N, Shimada M.** Cholangiolocellular carcinoma containing hepatocellular carcinoma and cholangiocellular carcinoma, extremely rare tumor of the liver:a case report. *J Med Invest.* 2008 Feb;55(1-2):161-5. Review.
2. **Goodman ZD.** Neoplasms of the liver. *Mod Pathol.* 2007 Feb;20 Suppl 1:S49-60.
3. **DeOliveira ML, Cunningham SC, Cameron JL, Kamangar F, Winter JM, Lillemoe KD, Choti MA, Yeo CJ, Schulick RD.** Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. *Ann Surg.* 2007 May;245(5):755-62.
4. **Vauthey JN, Blumgart LH.** Recent advances in the management of cholangiocarcinomas. *Semin Liver Dis.* 1994 May;14(2):109-14. Review.
5. **Jepsen P, Vilstrup H, Tarone RE, Friis S, Sørensen HT.** Incidence rates of intra- and extrahepatic cholangiocarcinomas in Denmark from 1978 through 2002. *J Natl Cancer Inst.* 2007 Jun 6;99(11):895-7.
6. **Patel T.** Increasing incidence and mortality of primary intrahepatic cholangiocarcinoma in the United States. *Hepatology.* 2001 Jun;33(6):1353-7.
7. **Henson DE, Albores-Saavedra J, Corle D.** Carcinoma of the extrahepatic bile ducts. Histologic types, stage of disease, grade, and survival rates. *Cancer.* 1992 Sep 15;70(6):1498-501.
8. **Sahani D, Prasad SR, Tannabe KK, Hahn PF, Mueller PR, Saini S.** Thorotrast-induced cholangiocarcinoma: case report. *Abdom Imaging.* 2003 Jan-Feb;28(1):72-4.
9. **Mecklin JP, Järvinen HJ, Virolainen M.** The association between cholangiocarcinoma and hereditary nonpolyposis colorectal carcinoma. *Cancer.* 1992 Mar 1;69(5):1112-4.
10. **Nakeeb A, Pitt HA, Sohn TA, Coleman J, Abrams RA, Piantadosi S, Hruban RH, Lillemoe KD, Yeo CJ, Cameron JL.** Cholangiocarcinoma. A spectrum of intrahepatic, perihilar, and distal tumors. *Ann Surg.* 1996 Oct;224(4):463-73; discussion 473-5.
11. **Chari S, Lowe R, Afdhal N, Anderson C.** Clinical manifestations and diagnosis of cholangiocarcinoma. *UpToDate* January 2008. This topic last updated: October 17, 2007.
12. **Mantel HT, Verdonk RC, van Dullemen HM, Gietema JA, Slooff MJ, Porte RJ.** [Diagnostics and treatment of cholangiocarcinoma] *Ned Tijdschr Geneeskd.* 2008 May 3;152(18):1037-41. Review. Dutch.
13. **Endo I, Gonen M, Yopp AC, Dalal KM, Zhou Q, Klimstra D, D'Angelica M, DeMatteo RP, Fong Y, Schwartz L, Kemeny N, O'Reilly E, Abou-Alfa GK, Shimada H, Blumgart LH, Jarnagin WR.** Intrahepatic cholangiocarcinoma: rising frequency, improved survival, and determinants of outcome after resection. *Ann Surg.* 2008 Jul;248(1):84-96.
14. **Lazaridis KN.** Sclerosing cholangitis epidemiology and etiology. *J Gastrointest Surg.* 2008 Mar;12(3):417-9. Epub 2007 Oct 24. Review.
15. **Talwalkar JA, Lindor KD.** Primary sclerosing cholangitis. *Inflamm Bowel Dis.* 2005 Jan;11(1):62-72. Review.
16. **Saich R, Chapman R.** Primary sclerosing cholangitis, autoimmune hepatitis and overlap syndromes in inflammatory bowel disease. *World J Gastroenterol.* 2008 Jan 21;14(3):331-7. Review.
17. **Tischendorf JJ, Hecker H, Krüger M, Manns MP, Meier PN.** Characterization, outcome, and prognosis in 273 patients with primary sclerosing cholangitis: A single center study. *Am J Gastroenterol.* 2007 Jan;102(1):107-14. Epub 2006 Oct 13.
18. **Levy C, Lindor KD.** Primary sclerosing cholangitis: epidemiology, natural history, and prognosis. *Semin Liver Dis.* 2006 Feb;26(1):22-30. Review.
19. **Michaels A, Levy C.** The medical management of primary sclerosing cholangitis. *Medscape J Med.* 2008 Mar 12;10(3):61. Review.
20. **Rabinovitz M, Gavaler JS, Schade RR, Dindzans VJ, Chien MC, Van Thiel DH.** Does primary sclerosing cholangitis occurring in association with inflammatory bowel disease differ from that occurring in the absence of inflammatory bowel disease? A study of sixty-six subjects. *Hepatology.* 1990 Jan;11(1):7-11.
21. **Bergquist A, Lindberg G, Saarinen S, Broomé U.** Increased prevalence of primary sclerosing cholangitis among first-degree relatives. *J Hepatol.* 2005 Feb;42(2):252-6.
22. **Loftus EV Jr, Sandborn WJ, Tremaine WJ, Mahoney DW, Zinsmeister AR, Offord KP, Melton LJ 3rd.** Primary sclerosing cholangitis is associated with nonsmoking: a case-control study. *Gastroenterology.* 1996 May;110(5):1496-502.
23. **van Erpecum KJ, Smits SJ, van de Meeberg PC, Linn FH, Wolfhagen FH, vanBerge-Henegouwen GP, Algra A.** Risk of primary sclerosing cholangitis is associated with nonsmoking behavior. *Gastroenterology.* 1996 May;110(5):1503-6.
24. **Mitchell SA, Thyssen M, Orchard TR, Jewell DP, Fleming KA, Chapman RW.** Cigarette smoking, appendectomy, and tonsillectomy as risk factors for the development of primary sclerosing cholangitis: a case control study. *Gut.* 2002 Oct;51(4):567-73.
25. **Beuers U, Spengler U, Kruis W, Aydemir U, Wiebecke B, Heldwein W, Weinzierl M, Pape GR, Sauerbruch T, Paumgartner G.** Ursodeoxycholic acid for treatment of primary sclerosing cholangitis: a placebo-controlled trial. *Hepatology.* 1992 Sep;16(3):707-14.
26. **Chazouillères O, Poupon R, Capron JP, Metman EH, Dhumeaux D, Amouretti M, Couzigou P, Labayle D, Trinchet JC.** Ursodeoxycholic acid for primary sclerosing cholangitis. *J Hepatol.* 1990 Jul;11(1):120-3.
27. **Stiehl A, Walker S, Stiehl L, Rudolph G, Hofmann WJ, Theilmann L.** Effect of ursodeoxycholic acid on liver and bile duct disease in primary sclerosing cholangitis. A 3-year pilot study with a placebo-controlled study period. *J Hepatol.* 1994 Jan;20(1):57-64.
28. **De Maria N, Colantoni A, Rosenbloom E, Van Thiel DH.** Ursodeoxycholic acid does not improve the clinical course of primary sclerosing cholangitis over a 2-year period. *Hepatogastroenterology.* 1996 Nov-Dec;43(12):1472-9.
29. **Lindor KD.** Ursodiol for primary sclerosing cholangitis. Mayo Primary Sclerosing Cholangitis-Ursodeoxycholic Acid Study Group. *N Engl J Med.* 1997 Mar 6;336(10):691- 5.

30. **van Hoogstraten HJ, Wolfhagen FH, van de Meeberg PC, Kuiper H, Nix GA, Becx MC, Hoek AC, van Houte DP, Rijk MC, Salemans JM, Scherpenisse J, Schrijver M, Smit AM, Spoelstra P, Stadhouders PH, Tan TG, Hop WC, ten Kate FJ, vanBerge-Henegouwen GP, Schalm SW, van Buuren HR.** Ursodeoxycholic acid therapy for primary sclerosing cholangitis: results of a 2-year randomized controlled trial to evaluate single versus multiple daily doses. *J Hepatol.* 1998 Sep;29(3):417-23.
31. **Harnois DM, Angulo P, Jorgensen RA, Larusso NF, Lindor KD.** High-dose ursodeoxycholic acid as a therapy for patients with primary sclerosing cholangitis. *Am J Gastroenterol.* 2001 May;96(5):1558-62.
32. **Mitchell SA, Bansi DS, Hunt N, Von Bergmann K, Fleming KA, Chapman RW.** A preliminary trial of high-dose ursodeoxycholic acid in primary sclerosing cholangitis. *Gastroenterology.* 2001 Oct;121(4):900-7.
33. **Gordon F.** Recurrent primary sclerosing cholangitis: Clinical diagnosis and long-term management issues. *Liver Transpl.* 2006 Nov;12(11 Suppl 2):S73-5. Review.
34. **Farrant JM, Hayllar KM, Wilkinson ML, Karani J, Portmann BC, Westaby D, Williams R.** Natural history and prognostic variables in primary sclerosing cholangitis. *Gastroenterology.* 1991 Jun;100(6):1710-7.
35. **Broomé U, Olsson R, Lööf L, Bodemar G, Hultcrantz R, Danielsson A, Prytz H, Sandberg-Gertzén H, Wallerstedt S, Lindberg G.** Natural history and prognostic factors in 305 Swedish patients with primary sclerosing cholangitis. *Gut.* 1996 Apr;38(4):610-5.
36. **Roberts MS, Angus DC, Bryce CL, Valenta Z, Weissfeld L.** Survival after liver transplantation in the United States: a disease-specific analysis of the UNOS database. *Liver Transpl.* 2004 Jul;10(7):886-97.
37. **Merion RM.** When is a patient too well and when is a patient too sick for a liver transplant? *Liver Transpl*. 2004 Oct;10(10 Suppl 2):S69-73. Review.
38. **Burak K, Angulo P, Pasha TM, Egan K, Petz J, Lindor KD.** Incidence and risk factors for cholangiocarcinoma in primary sclerosing cholangitis. *Am J Gastroenterol.* 2004 Mar;99(3):523-6.
39. **Levy C, Lymp J, Angulo P, Gores GJ, Larusso N, Lindor KD.** The value of serum CA 19-9 in predicting cholangiocarcinomas in patients with primary sclerosing cholangitis. *Dig Dis Sci.* 2005 Sep;50(9):1734-40.
40. **Björnsson E, Kilander A, Olsson R.** CA 19-9 and CEA are unreliable markers for cholangiocarcinoma in patients with primary sclerosing cholangitis. *Liver.* 1999 Dec;19(6):501-8.
41. **Silveira MG, Lindor KD.** Clinical features and management of primary sclerosing cholangitis. *World J Gastroenterol*. 2008 Jun 7;14(21):3338-49. Review.

Submitted on January 6, 2009