Case Report

Biliary Papillomatosis Coexisting with Hepatitis C: Report of a Rare Case with Review of the Literature

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Abstract

Biliary papillomatosis is a rare disease and is often fatal. It is characterized by diffuse papillary proliferations of bile duct epithelial cells. Patient may present with fever, abdominal pain and obstructive jaundice. The degree of biliary obstruction varies, ranging from almost asymptomatic to severe life-threatening illness with painful obstructive jaundice, vomiting, cholangitis, and pancreatitis. Preoperative diagnosis is very uncommon. Here, we describe an incidental finding of a case of biliary papillomatosis after liver transplant in a 65 year-old woman with end-stage liver disease secondary to Hepatitis C. Grossly, the mass is located at the posterior aspect of the right lobe, extending to the portal area, presenting as a white fibrotic area measuring 6.0 x 8.0 x 4.5 cm. Cut surface of this area is gray-white with multiple cysts ranging from 1.2 x 0.9 x 0.9 cm to 0.2 x 0.2 x 0.2 cm. Microscopic examination revealed glandular growth pattern of the epithelial cells with a stroma consisted of fibrovascular connective tissue. These epithelial cells have abundant cytoplasm with the nuclei arranged regularly close to the basement membrane. There is slight nuclear hyperchromatism, but there is no obvious atypia. The tumor cells contain mucin as shown by PAS stain, which is resistant to the diastase treatment. The negative immunohistochemical stains for CEA and Cytokeratin 20 did not support the possibility of metastatic tumor from lower GI tract, while the positive Cytokeratin 7 staining was compatible with an origin of intrahepatic bile duct. Based on above findings, she was diagnosed multifocal biliary papillomatosis in the background of florid bile ductule proliferation. The cirrhosis and chronic inflammation in her liver were consistent with the history of hepatitis C. She also had associated chronic cholecystitis and cholelithiasis. She was treated by liver transplantation. The patient is doing well now (eight years after the transplantation). In addition, the related literatures are reviewed, and the possible pathogenesis, treatment plan, and prognosis of biliary papillomatosis are briefly discussed.

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Key Words:

Biliary Papillomatosis, proliferations, Hepatitis C, gastroduodenoscopy

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Introduction

Intrahepatic biliary papillomatosis is a rare disorder, occurs mainly in men. [1-3] It is characterized by the presence of many multicentric papillomas of the biliary mucosa that project into lumen of the biliary tract. Clinically it is manifested by recurrent episodes of obstructive jaundice and cholangitis that result, in part, from the production of thick mucus by the tumor.[1-3] Since the first description by Chappet in 1894, only about 100 cases have been reported in the English literature. In several of the cases, a malignant transformation into invasive adenocarcinoma has been described.[4-6] We report a new case of papillomatosis coexisting with preexisting hepatitis C. To our knowledge, this is the fourth case of biliary papillomatosis coexisting with hepatitis C.[2,7,8]

Report of a Case

Patient is a 65 year-old female with end-stage liver disease secondary to Hepatitis C and cirrhosis. She has had hypertension for 20 years. In 1993, she presented with lower extremity edema, positive hepatitis C antibody, decreased albumin, elevated prothrombin time, AST(174), ALT (122), and total bilirubin (7.0). Her alpha fetoprotein, anti-nuclear antibody and iron studies were normal. She had no evidence of polyclonal gammopathy. Both abdominal CT and ultrasound demonstrated an enlarged spleen and a coarse liver without any focal masses. An esophago-

gastroduodenoscopy demonstrated trace varices and mild distal gastritis. An abdominal ultrasound was remarkable for gallstones and gallbladder wall thickening, suggesting cholecystitis. There was no abdominal pain, melena or hematemesis or any change in her weight. She was diagnosed chronic hepatitis C virus infection with cirrhosis.

Over the next several years, she gradually developed bilateral lower extremity edema, worsening thrombocytopenia, esophageal varices with portal gastropathy, and worsening hypoalbuminemia, worsening fatigue, and some short-term memory loss related to her chronic hepatic encephalopathy, and was put on liver transplant waiting list in 1997. A CT scan of the abdomen in September 2000 showed a small nodular liver with an abnormal area of decreased attenuation. In this area, there was central lucency which was new when compared with her previous scans. The MRI scan in May 2001 showed similar findings. The lesion was located at the posterior right lobe of the liver, and was thought to be a hepatoma. However, the biopsy failed to confirm this diagnosis. She underwent a living donor liver transplantation from her son on 05/24/2001, and was doing well now (eight years after the transplantation).

Pathologic Findings

The liver weighs 1,030 grams. The right lobe of liver measures 17.5 x 13.5 x 8.5 cm. The left lobe of liver measures 14.0 x 10.0 x 2.0 cm. The liver is firm and has multiple nodules ranging from 0.6 x 0.6 x 0.6 cm to 0.3 x 0.3 x 0.3 cm on its surface. The liver is bread-loafed revealing an ill-defined area of fibrosis measuring 6.0 x 8.0 x 4.5 cm located at the posterior aspect of the right lobe, extending to the portal area, partially occluding the entrance of the right intrahepatic duct. Cut surface of this area is gray-white with multiple cysts ranging from 1.2 x 0.9 x 0.9 cm to 0.2 x 0.2 x 0.2 cm. The cut surface of the rest of the liver is fibrotic with multiple small nodules ranging from 0.9 cm to 0.3 cm in diameter.

The gallbladder weighs 34 grams and measures 7.5 x 3.5 x 3.0 cm. The gallbladder contains multiple black gallstones ranging from 0.6 cm to 0.3 cm in diameter. Both mucosa surface and serosal surface of the gallbladder are grossly unremarkable.

Multiple representative sections of the liver and gallbladder were taken and stained with hematoxylin-eosin (H&E), PAS ± diastase, trichrome blue and elastic stains. Immunoperoxidase stains for CEA, Cytokeratin 7, and Cytokeratin 20 were performed on selected sections by avidin-biotin-peroxidase technique.

Under microscope, multiple papillomas are found in the expanded portal tracts. These papillomas are composed of glandular growth of well-differentiated cuboidal bile duct epithelium within loose connective tissue in a background of cirrhosis (**Figures 1** and **2**). These epithelial cells have abundant cytoplasm with the nuclei arranged regularly close to the basement membrane. The nuclei of the epithelial cells were slightly hyperchromatic without significant cytological atypia (**Figure 3**). These cells contain mucin as shown by PAS stain, which is resistant to the diastase treatment (**Figure 4**). The negative immunohistochemical stains for Cytokeratin 20 (**Figure 5**) and CEA (picture not shown) do not support the possibility of metastatic tumor from lower GI tract, while Cytokeratin 7 positivity (**Figure 6**) is compatible with an origin of intrahepatic bile duct. The rest of the liver is severely fibrotic. Representative sections from gallbladder show chronic inflammation (pictures not shown).

Final Diagnosis

Multifocal biliary papillomatosis is present in the background of florid bile ductule proliferation and end stage cirrhosis associated with hepatitis C. Gallbladder has chronic cholecystitis and cholelithiasis.

Discussion

Biliary papillomatosis is a rare condition with only about 100 cases reported in English literature. It is characterized by diffuse papillary proliferations of bile duct epithelia cells.[1,2] The lesion is similar to villous adenoma of the colon or mucinous ductal ectasia of the pancreas. These papillomas can be either benign or malignant.[1-3] It presents clinically as obstructive jaundice and biliary sepsis.[2,9-12] Here, we report the diagnosis of a patient with biliary papillomatosis with a successful liver transplantation, who was previously suspected for hepatoma based on CT and MRI scanning.

Biliary papillomatosis is slightly more common in men than women with an average age of 58 (ranging from 21-89). Patient may present with fever, abdominal pain and obstructive jaundice. The degree of biliary obstruction is varied, ranging from almost asymptomatic with elevated bilirubin and liver enzymes to severe life-threatening illness with painful obstructive jaundice, vomiting, cholangitis, and pancreatitis.[1-3] Preoperative diagnosis is very uncommon. Usually ultrasonography or CT show only distended intrahepatic and/or extra hepatic bile ducts and occasionally solid intraductal masses.[13] ERCP may provide important clues to the diagnosis.

Biliary papillomatosis has been reported to co-exist with the following diseases: ulcerative colitis, intrahepatic gallstones, choledochal cyst, hepatitis C, Caroli's disease and congenital hepatic fibrosis.[1-3,7,8,14] The results of lab tests are usually nonspecific with elevated total bilirubin, alkaline phosphatase, gammaglutamyl transpeptidase, and transaminase, consistent with biliary obstruction. Some cases of biliary papillomatosis were diagnosed by imaging studies, including Ultrasonography, CT scan, Endoscopic retragrade cholangiography, cholangioscopy, and endoscopic ultrasound.[6,13] Definitive diagnosis requires biopsy or resection. Common microscopic findings include multiple papillary structures covered by an unstratified cylindrical epithelium with fibrovascular connective tissue. The surface epithelium is composed of columnar or cuboidal cells, frequently exhibiting mucinous metaplasia.[1-3] The benign form shows basement membrane integrity, regular

monostratified papillary layer, and absence of mitosis. In the past, biliary papillomatosis was considered to be of low malignant potential. Various studies have shown a higher rate of malignant transformation[4-6] and the presence of carcinogenic indicators like K-ras mutation and over-expression of p53.[5-8] The malignant forms range from carcinoma in situ to invasive carcinoma. Mild fibrosis and lymphocytic infiltration may be present, mainly in the portal area. CEA and AFP usually show negative staining.

The pathogenesis of biliary papillomatosis has not been clarified. Possible causes include: long-term stimulation by stones, reactive hyperplasia, ectopic tissue, recurrent pyogenic cholangitis and congenital choledochal cyst.[2,3,8] We propose that chronic infection, such as hepatitis C, should be also considered as one of the possible causes. Further study is necessary.

The optimal therapy is not known due to the rarity of the disease. Local excision seemed to be inadequate because of high local recurrence rates which resulted in multiple surgeries in most of the patients and risk of malignant transformation. For lesions localized to one lobe, partial hepatectomy is advocated. The current recommended treatment for disseminated lesions is liver transplantation although this is rarely done.[9]

The prognosis for biliary papillomatosis is poor because of repeated cholangitis, progressive hepatic failure, and malignant transformation. The most common cause of death was biliary sepsis. The median survival of patients was less than 18 months with a 5-year survival rate of 12%.[2,9-12] In our case, the patient was treated by liver transplantation and is doing well now (eight years after the transplantation).

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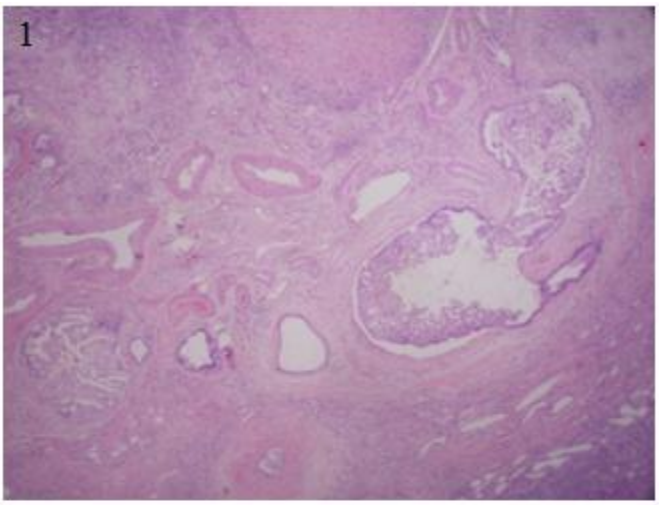
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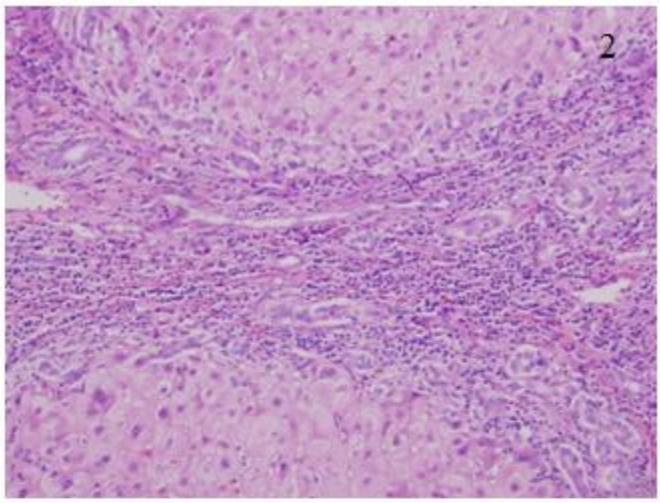
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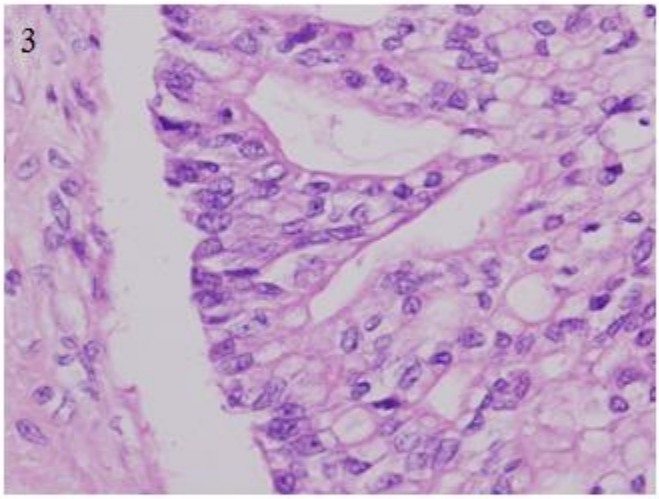
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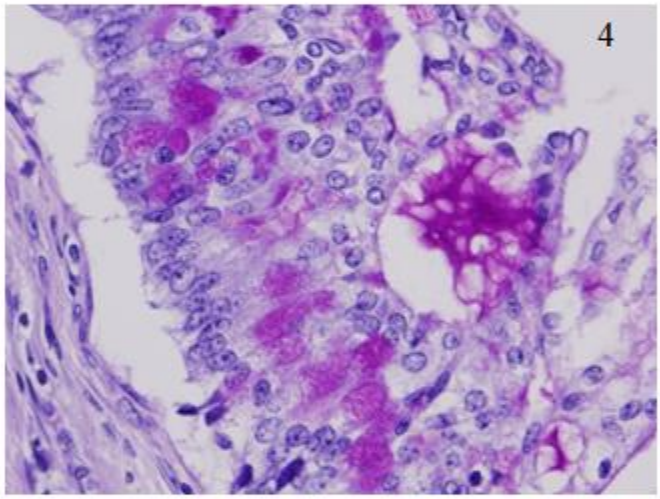
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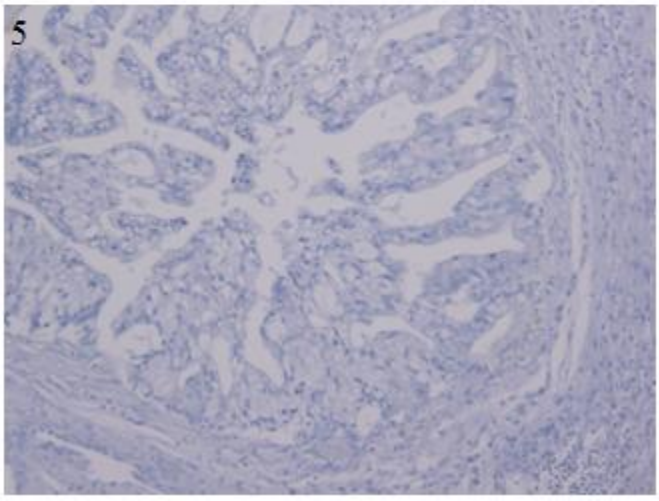
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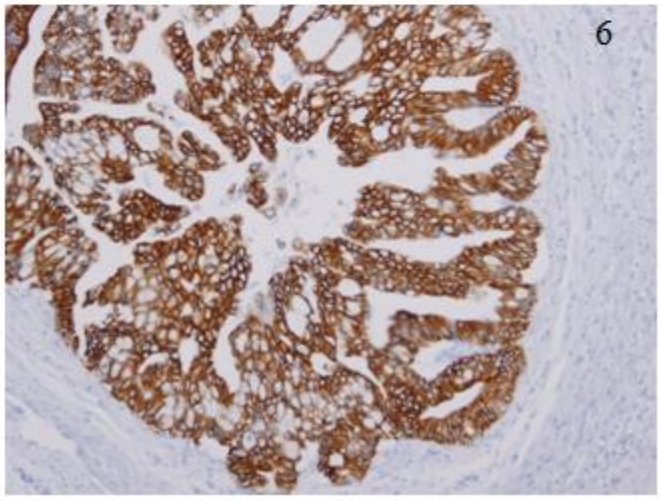
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