

Intrahepatic-ductal Papillary Mucinous Neoplasm: A Real Disease Entity

by Megha Kothari, Matthew Grossman, Gregory Haber

A 67 year-old Chinese female was referred for evaluation of recurrent right upper quadrant abdominal pain and fevers of approximately one year duration. Laboratory results showed no abnormalities except for a carcinoembryonic antigen (CEA) level of 206 ng/ml. Abdominal ultrasound revealed a 3 cm dilated common bile duct (CBD). Magnetic resonance cholangiopancreatography (MRCP) revealed intra and extra-hepatic ductal dilatation. An endoscopic retrograde cholangiopancreatography (ERCP) with direct cholangioscopy was performed showing a patulous ampulla with viscous mucin extravasating from the os. Cholangioscopy revealed papillary mucosal changes in the left intrahepatic duct. Multiple biopsies were taken from the area that revealed fibrous tissue with mild epithelial atypia. No malignant cells were identified. Given the possibility of an underlying papillary mucinous neoplasm, the patient was referred for a left hepatectomy with resection of the common bile duct. Surgical pathology revealed an intraductal papillary mucinous neoplasm (IPMN) with moderate epithelial dysplasia involving left hepatic duct and periductal branches. The patient had an uneventful recovery and was discharged six days after the procedure. Biliary intraductal neoplasms occur either as intra or extrahepatic lesions. A rare and recently emerging subtype of biliary intraductal neoplasms is intraductal papillary mucinous neoplasms of the bile duct (B-IPMN). They harbor a favorable outcome with aggressive surgical resection and they should be considered among the differential diagnosis when bile duct dilatation and hepatic parenchymal atrophy coexist. This area warrants further investigation to devise a classification system and treatment options.

INTRODUCTION

A rare and recently emerging papillary subtype of biliary intraductal neoplasms is intraductal pancreatic mucinous neoplasm of the bile duct (B-IPMN). B-IPMNs have histological and clinicopathological resemblance to pancreatic IPMNs. These rare tumors represent approximately 8.3-29.9% of all biliary neoplasms and more likely to occur in males between the ages of 39 and 71. Patients most commonly experience abdominal discomfort (65%), jaundice (39%) and weight loss (35%), which are related to mass effect. In comparison to pancreatic IPMN, B-IPMN have a greater malignancy potential, 83% vs. 30%. However, they harbor a favorable outcome with aggressive surgical resection.

Case Presentation

A 67 year-old Chinese female was referred to our center with recurrent right upper quadrant abdominal pain and intermittent fevers over the past year, worsening in the last month. Her history included a cholecystectomy 16 years ago for symptomatic gallstones. The patient's labs were within normal limits, except for an elevated carcinoembryonic antigen (CEA) level of 206 ng/ml (normal range 0-3 ng/ml). An initial abdominal ultrasound revealed a markedly dilated common bile duct (CBD) to approximately 3 cm. Magnetic resonance cholangiopancreatography (MRCP) confirmed intra and extra-hepatic duct dilatation with a fusiform CBD measuring 2.8 cm (Image 1 and 2). No intrahepatic bile duct or CBD calculi were identified. Marked

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saccular dilatation of intra-hepatic bile ducts was seen in the lateral segment of the left lobe (segments 2 and 3). No pancreatic mass or pancreatic ductal abnormality was noted. An endoscopic retrograde cholangiopancreatography (ERCP) with direct cholangioscopy (Spyglass, Boston Scientific) was performed. The ampulla was noted to have a classic “fish-mouth” appearance – patulous with viscous mucin extravasating from the os. ERCP revealed papillary mucosal changes in the left intrahepatic duct near the saccular dilatation (Image 3). Multiple cold-forcep biopsies were taken from the area. Pathology noted fibrous tissue with mild epithelial atypia. No carcinoma was identified. Given the findings, there was concern for an underlying papillary mucinous neoplasm and the patient was then referred for a left hepatectomy with resection of the common bile duct. Surgical pathology revealed a biliary intraductal papillary mucinous neoplasm (B-IPMN) with moderate epithelial dysplasia involving the left hepatic duct and periductal branches (Images 4-7).

Discussion

Biliary intraductal neoplasms are found to occur as either intra or extrahepatic lesions. A rare and recently emerging papillary subtype of biliary intraductal neoplasms is IPMN of the bile duct (B-IPMN). The two known subtypes are flat and papillary type.¹ However, B-IPMN have histological and clinicopathological resemblance to pancreatic IPMN. This is believed to be in part due to parallel embryological developments of the pancreatic and bile ducts from the hepato-pancreatic bud of the foregut.² B-IPMN differ from other biliary mucinous cystic neoplasms; they lack ovarian-like

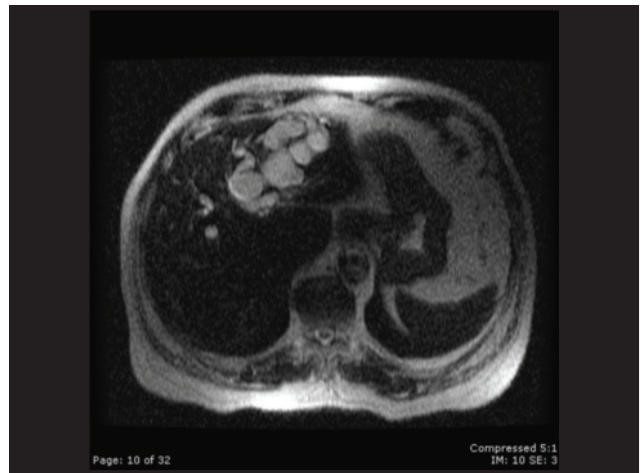


Image 1. T2 weighted MRI image showing marked saccular dilatation of the left lobe intrahepatic bile ducts and associated hepatic parenchymal atrophy.

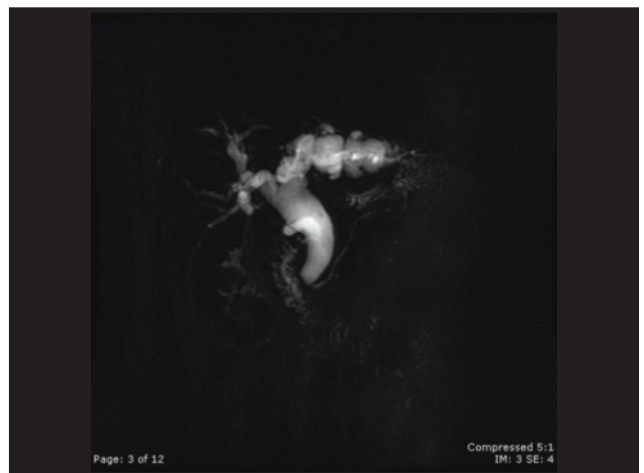


Image 2. Highly T2 weighted MRI image showing marked saccular dilatation of left lobe intrahepatic bile ducts and the common bile duct showing marked fusiform dilatation measuring up to 2.8-cm diameter.



Image 3. ERCP showing papillary mucosal changes in the left intrahepatic duct near the saccular dilatation.

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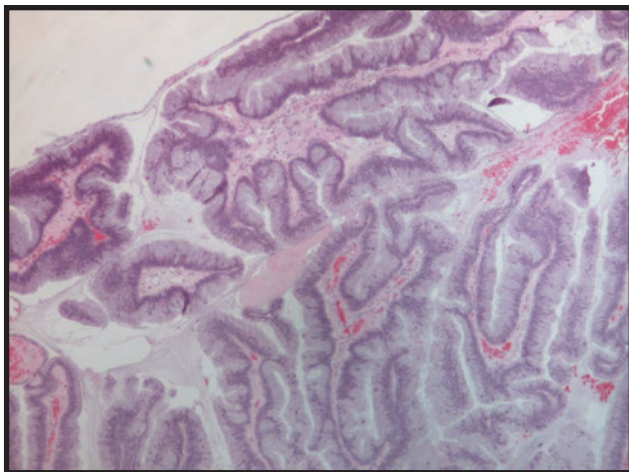


Image 4. At low power, the ducts are filled with variably complex papillary projections lined by tall, columnar mucinous epithelial cells. (10X magnification)

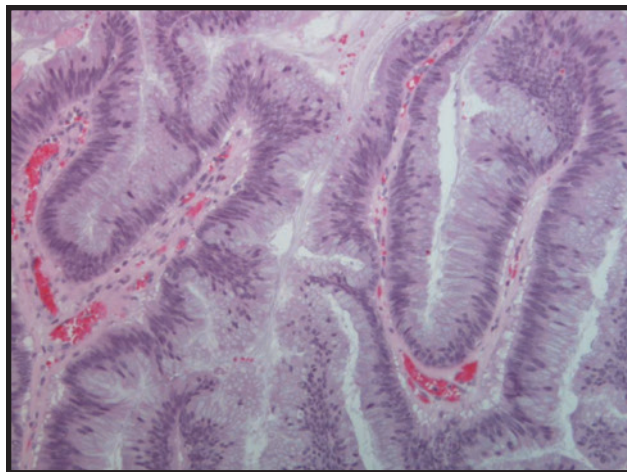


Image 5. On high power, the papillae are long and villiform. The nuclei are elongated and show a variable degree of pseudostratification and intracellular mucin with moderate epithelial dysplasia. The papillae resemble villous adenomas of the large bowel. (40X magnification)

stroma and growth tends to occur along the biliary ducts, without confined cyst formation.³

These rare tumors represent approximately 8.3-29.9% of all biliary neoplasms.⁴ The wide range is likely due to variations in classification of B-IPMN.⁴ In a retrospective study of resected cholangiocarcinomas, Chu et al. found that B-IPMN are more frequently encountered in males between the ages of 39 and 71.⁴ A high correlation of B-IPMN is observed in patients with a history of choledocholithiasis, infections, pancreatic injury and biliary hyperplasia thus potentially defining some of the risk factors.¹ These lesions are thought to develop from stem cells of the bile ductules, lining of biliary epithelium glands or epithelium of peribiliary glands.⁵

Although very little is known regarding the molecular pathogenesis of the B-IPMN, the idea of microsatellite instability has been postulated. Susan et al. extracted DNA samples from B-IPMN lesions, invasive cholangiocarcinoma and normal tissue to find high occurrence microsatellite instability, particularly in B-IPMN. Importantly, they noted that the patterns of allelic shifts were different between relatively benign IPMN and invasive cholangiocarcinoma lesions, indicating a high level of genetic heterogeneity in these neoplasms.⁶ This variation may in part contribute to their difference of varying malignant potentials.

B-IPMN exhibit mucosal spread along the bile duct lumen and cause mucin hypersecretion, often resulting in polypoid or sessile growths;^{3,5} therefore, ducts may

exhibit marked dilatation. Tumors are often confined within the dilated part of the bile ducts.³ Occasionally, hepatic parenchymal atrophy has been observed due to long-standing elevated ductal pressures, resulting in partial obstruction.⁵ This may be accompanied by compensatory hypertrophy of a “normal” hepatic lobe.⁵ However, mass effect related symptoms may not always be present with B-IPMN. Symptoms usually appear when a mass enlarges to cause pressure on the liver capsule.⁵ Lim et al. reported that the most common symptom presentations are abdominal discomfort (65%), jaundice (39%) and weight loss (35%).⁷

In comparison to pancreatic IPMN, B-IPMN had a greater malignancy potential, 83% vs. 30%.² B-IPMN range from benign to malignant based on histological criteria. One classification scheme categorizes the tumors as adenomas, borderline tumors, carcinoma in situ or carcinomas.¹ Another classification system is based on histology and genetic expression, which has significant roles in carcinogenesis and tumor invasion. Histologically, B-IPMN can be classified as intestinal, pancreato-biliary, gastric or oncocytic; while gene expression is classified as MUC1, MUC2, and MUC5 genes.¹ Higashi et al. found that MUC1 expression and the absence of MUC2 correlated with increased aggressiveness and subsequently a poor outcome in pancreatic ductal adenocarcinomas. Subsequently, isolated MUC2 and MUC5 expression poses a more favorable outcome for B-IPMNs.^{1,5,8}

Ultrasound and MRCP are the initial non-invasive

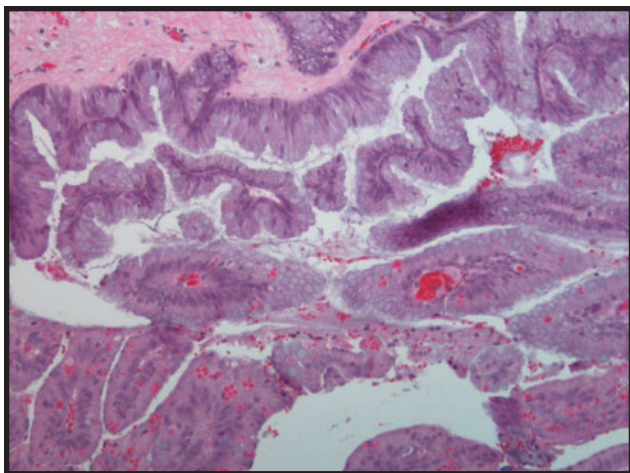


Image 6. At low power, the ducts are filled with variably complex papillary projections lined by tall, columnar mucinous epithelial cells. (10X magnification)

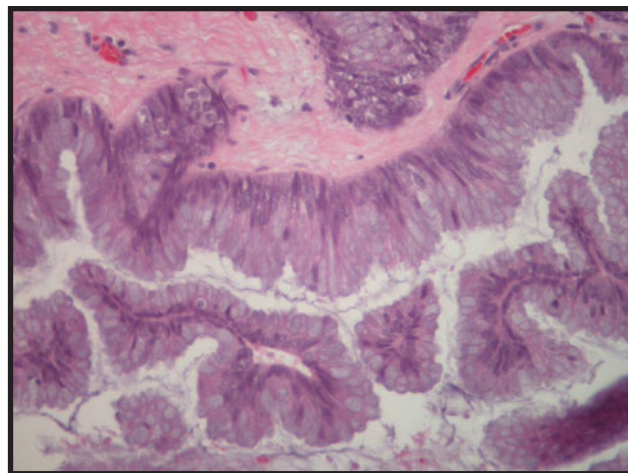


Image 7. On high power, the papillae are long and villiform. The nuclei are elongated and show a variable degree of pseudostratification and intracellular mucin with moderate epithelial dysplasia. The papillae resemble villous adenomas of the large bowel. (40X magnification)

studies for assessment of IPMN lesions. It is important to note that ERCP fails to delineate intraductal papillary changes along the ductal border; thus, cholangioscopy and/or intraductal ultrasonography (IDUS) are the most sensitive and specific modalities for diagnosing and localizing papillary tumors. The presence of a large amount of viscous mucin within the duct can make cholangiogram imaging difficult. Cholangioscopy proves to be better than IDUS to diagnose the extent of tumor.⁹

A recent case report presented a large B-IPMN, which was resected via a right sided trisectionectomy and caudate lobectomy.¹⁰ The authors note that complete surgical resection usually has a favorable prognosis; therefore, aggressive surgery needs to be recommended regardless of tumor size and extent.¹⁰ Favorable prognosis of B-IPMN is likely due to the theory that these tumors do not aggressively invade the bile duct wall unless there is transformation to tubular adenocarcinoma or mucinous adenocarcinoma.¹¹

CONCLUSION

In conclusion, B-IPMN are rare neoplasms which harbor a favorable outcome with aggressive surgical resection. Biliary mucinous cystic neoplasm, mass-forming type intrahepatic cholangiocarcinoma with choledochal cysts and recurrent pyogenic cholangitis with choledocholithiasis are among the differentials for B-IPMN lesions.⁹ However, biliary IPMN should be considered when bile duct dilatation and hepatic

parenchymal atrophy is seen. This area warrants further investigation to devise a classification system and treatment options. ■

References

1. Yaman B, Nart D, Yilmaz F, et al. "Biliary intraductal papillary mucinous neoplasia: three case reports." *Virchows Archiv*. 2009 May;454(5):589-94.
2. Barton, J, Barrett D, Maricevich M, et al. "Intraductal papillary mucinous neoplasm of the biliary tract: a real disease?" *HPB (Oxford)*. 2009 Dec; 11(8):684-91.
3. Takanami K, Yamada T, Tsuda M, et al. "Intraductal papillary mucinous neoplasm of the bile ducts: multimodality assessment with pathologic correlation." *Abdominal Imaging*. 2011 Aug;36(4):447-56.
4. Chu C, Felbel W, Chu F. "Intrahepatic biliary intraductal oncocytic papillary neoplasm/carcinoma: first reported case in Australia and Literature review." *Radiology Case Reports*. [Online] 2007; 2:95.
5. Lim JH, Jang KT, Choi D. "Biliary intraductal papillary-mucinous neoplasm manifesting only as dilatation of the hepatic lobar or segmental bile ducts: imaging features in six patients." *American Journal of Roentgenology*. 2008 Sep;191(3):778-82
6. Abraham SC, Lee JH, Boitnott JK, et al. "Microsatellite Instability in Intraductal Papillary Neoplasms of the Biliary Tract." *Modern Pathology*. 2002;15(12):1309-1317
7. Lim JH, Zen Y, Jang KT, et al. "Cyst-forming intraductal papillary neoplasm of the bile ducts: description of imaging and pathologic aspects." *American Journal of Roentgenology*. 2011 Nov; 197 (5): 1111-20.
8. Yonezawa S, Higashi M, Yamada N, et al. "Significance of mucin expression in pancreaticobiliary neoplasms." *J Hepatobiliary Pancreat Sci*. 2010 Mar;17(2):108-24. Epub 2009 Sep 29.
9. Tsuyuguchi T, Sakai Y, Sugiyama H, et al. "Endoscopic diagnosis of intraductal papillary mucinous neoplasm of the bile duct." *J Hepatobiliary Pancreat Sci*. 2010 May; 17(3):230-5
10. Sohn WJ, Jo S. "A huge intraductal papillary mucinous carcinoma of the bile duct treated by right trisectionectomy with caudate lobectomy." *World J Surg Oncol*. 2009 Dec 5;7:93.
11. Takanami K, Yamada T, Tsuda M, et al. "Intraductal papillary mucinous neoplasm of the bile ducts: multimodality assessment with pathologic correlation." *Abdominal Imaging*. 2011 Aug; 36(4):447-56.