

Intraductal papillary neoplasm of the bile duct : case report and review of the literature

P. Apostolopoulos¹, K. A. Ekmektzoglou¹, K. Paraskeva², K. Dimopoulos¹, K. Paparaskeva³, G. Alexandrakis¹

(1) Department of Gastroenterology, Army Share Fund Hospital (NIMTS), Athens, Greece ; (2) Department of Gastroenterology, "Konstantopoulio" General Hospital, Nea Ionia, Attica, Greece ; (3) Department of Histopathology, "Konstantopoulio" General Hospital, Nea Ionia, Attica, Greece.

Abstract

A variant of bile duct carcinoma, intraductal papillary neoplasm of the bile duct (IPNB) is a rare disease mainly found in Eastern Asia which encompasses a spectrum of intraductal papillary growth occurring anywhere along the intrahepatic and/or extrahepatic biliary tree that carries a high potential for malignancy. We report the case of a patient with episodes of recurrent cholangitis that was diagnosed with IPNB, our clinical and diagnostic approach, the radiographic and endoscopic findings, the interventions used, while discussing the therapeutic options. (*Acta gastroenterol. belg.*, 2018, 81, 97-99).

Key words : intraductal papillary neoplasm of the bile duct, biliary papillomatosis, treatment.

Introduction

A variant of bile duct carcinoma, biliary papillomatosis or intraductal papillary neoplasm of the bile duct (IPNB) is a rare disease mainly found in Eastern Asia as a consequence of increased prevalence of hepatolithiasis and clonorchiasis (1). With only approximately 150 cases reported worldwide (2), this disorder encompasses a spectrum of intraductal papillary growth occurring anywhere along the intrahepatic and/or extrahepatic biliary tree that carries a high potential for malignancy (1). Known over the years with several names (biliary papillomatosis, papillary adenoma, mucin-hypersecreting cholangiocarcinoma, etc.), the World Health Organization in its latest "classification of tumours of the digestive system" adopted the term IPNB so as to include intraductal papillary cholangiocarcinoma along with its precursor lesions (3). IPNB involves the intrahepatic ducts alone (9%), the extrahepatic ducts alone (58%), while 33% of patients have both extra- and intrahepatic ducts involvement (4).

We report the case of a patient with episodes of recurrent cholangitis that was diagnosed with IPNB, our clinical and diagnostic approach, the radiographic and endoscopic findings, the interventions used, while discussing the therapeutic options.

Case report

An 84 year old patient with jaundice, accompanied by an episode of acute cholangitis, presented in the Department

of Gastroenterology of the Army Share Fund Hospital (NIMTS) in September 2014. His past medical history included type non-insulin dependent diabetes mellitus (under metformin) and left sided nephrectomy (35 years ago due to neglected ureterolithiasis). A careful history revealed symptoms of painless jaundice 10 days before admittance (pale stools, dark urine, and pruritus). His clinical examination revealed a yellowish discoloration of the skin, conjunctivae, and mucous membranes, as well as mild tenderness upon palpation of the abdominal right upper quadrant. His initial laboratory values were the following: total bilirubin (tbil): 6,83mg/dl, direct bilirubin (dbil) : 5,51mg/dl, alkaline phosphatase (ALP) : 429IU/L, γ -glutamyl transferase (γ -GT) :151IU/L, aspartate aminotransferase (AST) : 104IU/L, and alanine aminotransferase (ALT) : 99IU/L. The patient was put on *iv* antibiotics (ciprofloxacin and metronidazole) while awaiting for the results of our diagnostic workup.

Both the abdominal ultrasound (US) and the magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) that followed revealed dilation of the common bile duct (CBD) and the intra- and extrahepatic bile ducts. The diffusely dilated CBD (18mm) was filled with multiple echogenic masses (US) and multiple materials of intermediate signal intensity, pointing to multiple choledocholithiasis (MRCP).

The endoscopic retrograde cholangiopancreatography (ERCP) confirmed the US/MRCP findings revealing a diffusely dilated CBD along with dilated intrahepatic ducts; multiple polylobed filling defects were depicted in the CBD (Figure 1). An endoscopic sphincterotomy was performed, with the balloon retrieving friable, polypoid soft tissue whitish masses from the bile ducts. After collecting tissue samples for histology, a biliary plastic stent was placed. The patient had an uneventful recovery getting discharged 2 days later.

The results of the histopathology report that were made public to us a few days later revealed intraductal

Correspondence to : Konstantinos Ekmektzoglou, 21 Nymphon Street, Gerakas 15344, Attica, Greece. Tel/Fax: +32106002820.
E-mail : ekmektzo@hotmail.com.

Submission date : 28/04/2016
Acceptance date : 02/09/2016

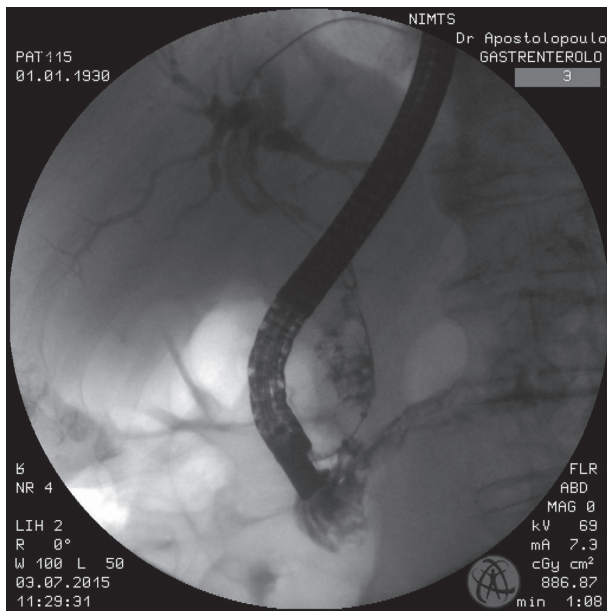


Figure 1. — The ERCP radiologic findings revealing multiple polylobed filling defects in a widely diffused CBD.

papillary neoplasm, pancreatobiliary type, with low-grade epithelial dysplasia (Figure 2).

The patient was readmitted in March 2015 (6 months after his initial consultation in our Department) due to a new episode of acute cholangitis. While being on *iv* antibiotics (ciprofloxacin and metronidazole) once more, the patient was referred to the Department of Gastroenterology of the “Konstantopoulou” General Hospital, where cholangioscopy, using the SpyGlass® direct visualization system (Boston Scientific), was performed in an attempt to delineate the extent of the disease. The cholangioscopy showed multiple polypoid soft tissue whitish masses throughout the extrahepatic ducts, sparing the intrahepatic ducts (Figure 3); the lumen of the plastic stent that was placed beforehand was plugged by a thick viscous material (mucin). After a thorough cleaning of the biliary tree, a partially covered 80mm x 10mm metal biliary stent was inserted (WallFlex Biliary RX, Boston Scientific). The patient returned to our Hospital and was discharged a few days later; his laboratory values soon returned to normal with his clinical recovery being, once again, uneventful.

Nearly a year from his second discharge, the patient has been having regular consultations in the Outpatient Office of our Department with satisfactory clinical outcome.

Discussion

Although considered the biliary counterpart of the pancreatic intraductal papillary mucinous neoplasm, IPNB does not seem to share its molecular pathways (5). IPNB specimens express cytokeratin 7, 20 and mucin 5AC; perhaps, IPNB tumor cells retain a biliary immunophenotype which later on during oncogenesis

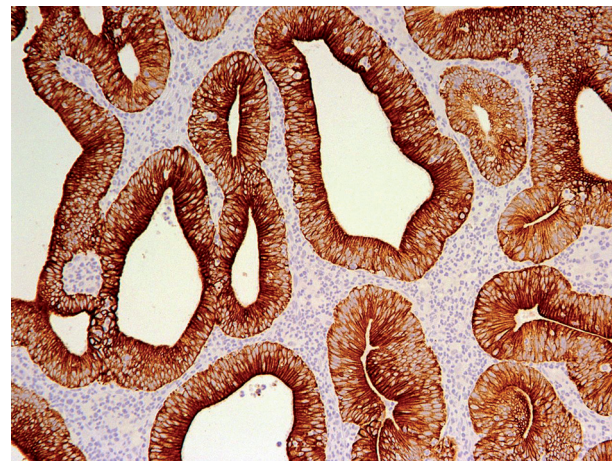


Figure 2. — Intraductal papillary neoplasm of the bile ducts, with low grade epithelial dysplasia and positivity to CK7 in immunohistochemistry (x 200).

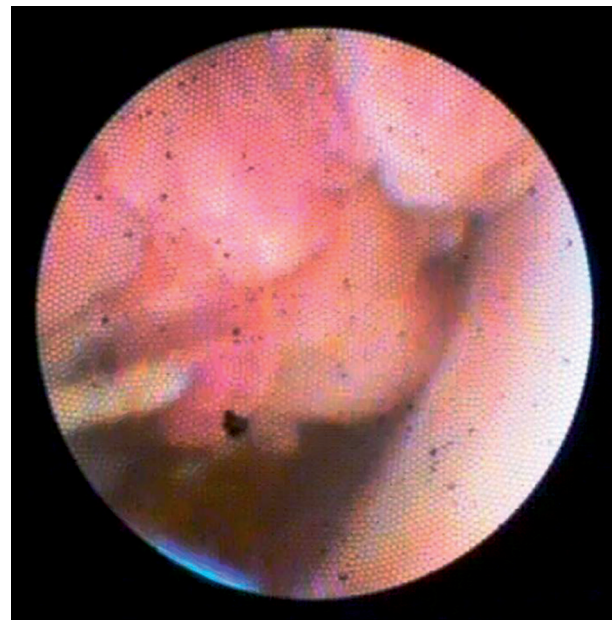


Figure 3. — Cholangioscopy showing multiple polypoid soft tissue whitish masses throughout the extrahepatic ducts.

gives way to intestinal and gastric immunophenotypes (1).

Many researchers have adopted 4 different histological epithelial subtypes (intestinal, gastric, pancreatobiliary and oncocytic). However, their prognostic differences have only been validated for pancreatic tumors (6). Another histological classification of IPNB takes into account the degree of nuclear and structural atypia along with the presence or not of invasion (7).

IPNB is classified according to its ability to secrete mucin as 1) mucin-hypersecreting type (MBP) or 2) non mucin-producing type (NMBP). In one of the most extensive review of 58 IPNB patients, overall survival (OS) rates of NMBP and MBP at 1 year were 89% and 69%, at 3 years 57% and 37%, and at 5 years 52% and 19%, respectively. A mean duration of 24 months

follow-up revealed a mean survival period of 52.27 ± 6.72 months for NMBP and 30.84 ± 8.36 months for MBP patients. No differences were found in survival rates amongst the two groups (7).

A patient with IPNB often presents with recurrent episodes of abdominal colic, intermittent obstructive jaundice, and repeated episodes of acute cholangitis. Besides, a friable tumor embolus can detach with great ease from its origin, leading to an acute obstruction of the bile duct that resembles bile duct stone obstruction. Last but not least, excess mucin within the bile ducts may occasionally impede bile flow leading to bile duct inflammation or abscess. As expected, acute cholangitis is more common in patients with MBP as a result of mucobilia (7).

Radiologic diagnosis of IPBN can be challenging. Ductal evaluation by ERCP or percutaneous transhepatic cholangiography (PTC) can be suboptimal in MBP patients for 2 reasons. First, MBP can cause obstruction and, therefore, prevent the opacification of the entire biliary tract. Secondly, mucin can inhibit the adequate inflow of the contrast material into the bile ducts; small papillomas can be missed by conventional radiologic modalities (8).

On cholangioscopy, the endoscopist encounters multiple soft, friable papillary masses (sometimes with normal mucosa in between) of pink or bright yellow color. Very often, they are covered by sludge material intermingled with pus. For MBPs, intraductal whitish or bile-tinged color mucin covering papillary mucosal lesion can be found (7).

Researchers report rates of malignant transformation from 41% to 83% (7,9). Surgery is considered the cornerstone of treatment, with partial hepatectomy (for localized disease) and liver transplantation along with pancreaticoduodenectomy (for extensive disease or recurrent IPBN) being the therapeutic options (1,7,10). However, surgery offers a small OS advantage. Yeung *et al.* reported an OS of less than 11 months, when IPBN was left untreated. On the contrary, the mean OS was 28 months when surgery was offered as a treatment option (9). This high recurrence rate could be attributed to either an incomplete preoperative evaluation of the extent of the disease or to positive resection margins (7,8). Some

researchers propose that the histopathological report of the resected specimen (giving data on tumor invasion and lymph node involvement) could stratify patients in need of more radical surgical treatment (11).

Regarding our patient, although IPBN is confined to the extrahepatic ducts, his advanced age, along with his expressed wish not to choose surgery, renders palliation (with stent insertion) the only practical treatment option. His performance status may be excellent with the patient carrying no significant comorbidities but one (diabetes mellitus); however, as clearly explained in his detailed surgical consultation, any surgical attempt carries a significant mortality risk. The patient has regular clinical, laboratory and imaging follow-ups due to the increased potential for malignancy.

References

1. WAN X.S., XU Y.Y., QIAN J.Y., YANG X.B., WANG A.Q., HE L. et al. Intraductal papillary neoplasm of the bile duct. *World J. Gastroenterol.*, 2013, **19** : 8595-604.
2. JOOSE M.E., SCHIPPER M.E., LIBBRECHT L., VAN BUUREN H.R., DE MAN R.A. Recurrent cholangitis in a 65-year-old man. Biliary papillomatosis. *Gut*, 2015, **64** : 883.
3. BOSMAN F.T., CARNEIRO F., HRUBAN R.H., THEISE N.D. WHO classification of tumours of the digestive system. 4th ed. Lyon : IARC, 2010 : 417.
4. CHUNG D.J., LEE S.K., HA H.K., KIM P.N., LEE M.G. Multiple biliary papillomatosis: comparison of MR cholangiography with endoscopic retrograde cholangiography. *J. Comput. Assist. Tomogr.*, 2002, **26** : 968-74.
5. KLÖPPEL G., KOSMAHL M. Is the intraductal papillary mucinous neoplasia of the biliary tract a counterpart of pancreatic papillary mucinous neoplasm? *J. Hepatol.* 2006, **44** : 249-50.
6. FURUKAWA T., HATORI T., FUJITA I., YAMAMOTO M., KOBAYASHI M., OHIKE N. et al. Prognostic relevance of morphological types of intraductal papillary mucinous neoplasms of the pancreas. *Gut*, 2011, **60** : 509-16.
7. LEE S.S., KIM M.H., LEE S.K., JANG S.J., SONG M.H., KIM K.P. et al. Clinicopathologic Review of 58 Patients with Biliary Papillomatosis. *Cancer*, 2004, **100** : 783-93.
8. YOON J.H. Biliary Papillomatosis: Correlation of Radiologic Findings with Percutaneous Transhepatic Cholangioscopy. *J. Gastrointest. Liver Dis.*, 2013, **22** : 427-33.
9. YEUNG Y.P., AHCHONG K., CHUNG C.K., CHUN A.Y. Biliary papillomatosis: report of seven cases and review of the English literature. *J. Hepatobiliary Pancreat. Surg.*, 2003, **10** : 390-5.
10. VASSILIOU I., KAIRI-VASSILATOU E., MARINIS A., THEODOSIOPOULOS T., ARKADOPoulos N., SMYRNIOTIS V. Malignant potential of intrahepatic biliary papillomatosis : a case report and review of the literature. *World J. Surg. Oncol.*, 2006, **4** : 71.
11. VIBERT E., DOKMAK S., BELGHITI J. Surgical strategy of biliary papillomatosis in Western countries. *J. Hepatobiliary Pancreat. Sci.*, 2010, **17** : 241-5.