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# Spread of Intraductal Papillary Neoplasm Arising from the Cystic Duct of the Biliary Tree

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## Keywords

Intraductal papillary neoplasm of the bile duct · Intraductal papillary neoplasm · Cystic duct

## Abstract

Intraductal papillary neoplasm of the bile duct (IPNB) is a variant type of the bile duct carcinoma characterized by intraductal growth. IPNB is also recognized as a precursor of invasive carcinoma. We describe herein an extremely rare case of IPNB arising from the cystic duct. A 68-year-old man was admitted to our hospital for investigation of epigastralgia and abnormal levels of biliary tract enzyme. Computed tomography and magnetic resonance imaging showed a mass lesion spreading from the cystic duct to the upper-middle bile duct. Endoscopic retrograde cholangiography demonstrated diffuse duct dilation with a grossly visible intraductal mass and amorphous blobs, suggesting the presence of mucobilia or scattered tumors. We performed extrahepatic bile duct resection with lymphadenectomy. Macroscopically, a friable papillary tumor originated from the cystic duct grows intraluminally into the bile duct. Pathologically, the tumor was found to be intramucosal adenocarcinoma spreading to the whole extrahepatic bile duct, which was compatible with IPNB. We should discuss the features and progression processes of IPNB through this precious case.

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## Background

Recently, the intraductal papillary neoplasm of the bile duct (IPNB) characterized by intraductal papillary growth of neoplastic biliary epithelia with a fine fibrovascular stalk has attracted attention as a novel disease concept. IPNB was recognized as a precancerous and early neoplastic lesion by the World Health Organization (WHO) tumor classification of the digestive system released in 2010 [1]. Additionally, IPNB is important as the biliary counterpart of intraductal papillary mucinous neoplasm (IPMN) of the pancreas. Immunohistochemical profiling of the mucin core (MUC) proteins is used to classify IPNB into four histologic subtypes, namely, pancreatobiliary type, intestinal type, gastric type, and oncocytic type [2, 3]. The relationship of malignant grade and subtype is interesting, but it is still unclear. According to previous reports, the vast majority of IPNs of the gallbladder have a pancreatobiliary type, whereas our case showed a mixture of several types. Our experience may lead to a better understanding and further studies of IPNB.

## Case Presentation

A 68-year-old man was referred to our hospital for investigation of epigastralgia and abnormal levels of biliary tract enzyme. He had repeated episodes of acute cholangitis; however, accurate diagnosis was still not made. On physical examination, no jaundice was revealed. He had tenderness in the right upper quadrant of the abdomen. Vital signs were: body temperature, 36.7°C; pulse, 73 beats per min; respiratory rate, 18 per min, and blood pressure, 114/75 mm Hg. The laboratory data on admission were as follows: white blood cell count, 5,300/ $\mu$ l; red blood cell count,  $403 \times 10^4$ / $\mu$ l; hemoglobin, 12.7 g/dl; hematocrit, 37.4%; platelets,  $18.5 \times 10^4$ / $\mu$ l; total bilirubin, 1.1 mg/dl; aspartate aminotransferase, 498 IU/l; alanine aminotransferase, 246 IU/l; alkaline phosphatase, 854 IU/l;  $\gamma$ -glutamyl transferase, 1,020 IU/l; blood urea nitrogen, 23.5 mg/dl; creatinine, 1.01 mg/dl; C-reactive protein, 0.18 mg/dl; CEA, 0.1 ng/ml, and CA19–9, 25.8 U/ml. Computed tomography of the abdomen revealed a soft-density mass contiguously developed from the gallbladder neck to the upper-middle bile duct. The boundaries of the mass seemed to be clear (fig. 1). Magnetic resonance cholangiopancreatography indicated diffuse dilation of the intrahepatic bile duct and the common hepatic duct (fig. 2). Endoscopic retrograde cholangiopancreatography (ERCP) directly showed the mass spreading from the cystic duct to the upper-middle bile duct with amorphous filling defect, suggesting the presence of mucobilia (fig. 3). The result of aspiration and exfoliative cytology during ERCP was class III. Based on these findings, we diagnosed gallbladder cancer arising from the cystic ducts with papillary expanding to the upper-middle bile duct. We planned to perform cholecystectomy and combined resection of the extrahepatic bile duct with regional lymphadenectomy. First of all, we made a transverse incision in the common hepatic duct in which a cauliflower-like mass coming off the bile duct lumen was obtained. Microscopic examination of the frozen section showed well-differentiated adenocarcinoma including papillary formation. Next, the planned operative procedure was performed (fig. 4). Although the bile duct lumen showed normal appearance in the resected proximal and distal stumps, superficial spread of carcinoma cells were microscopically existed. No cancer cells were eventually recognized by the additional resection at the biliary bifurcation and the intrapancreatic bile duct.

Unfortunately we are not able to show the complete original shape of the surgically resected specimen because the tumor was fragile and detached from the cystic duct lumen

during the operation; however, we confirmed that the papillary tumor was arising from the cystic duct (fig. 5). Histologic finding showed well-differentiated adenocarcinoma, which was superficially extending from the cystic duct to the epithelium of the whole extrahepatic bile duct (fig. 6). There was no regional lymph node metastasis expectedly. Immunohistochemical examination revealed that MUC1 and CDX2 were positive but MUC2, MUC5AC and MUC6 were negative in the papillary region. Meanwhile, MUC5AC and MUC6 were positive but MUC1, MUC2, and CDX2 were negative in the flat region (fig. 7). The tumor was finally diagnosed as well-differentiated adenocarcinoma arising from IPNB originated from the cystic duct with superficial spreading. The postoperative course was uneventful.

## Discussion

IPNB is characterized by mucus production and papillary proliferation of the bile duct epithelium in the dilated biliary lumen [3]. It is only in more recent times that the disease concept has been noted. IPNB is generally accepted as the biliary counterpart of intraductal papillary mucinous neoplasm (IPMN) of the pancreas [2, 4]. The neoplastic cells of IPNB and IPMN of the pancreas are usually classified into four phenotypes [2, 5]: (a) pancreatobiliary type, composed of columnar cell with an eosinophilic or pale eosinophilic cytoplasm and round nucleus; (b) the intestinal type, composed of stratified tall columnar cells, occasionally with goblet cells; (c) the gastric type, composed of columnar cells with abundant intracytoplasmic mucin and a clear cytoplasm; (d) the oncocytic type, a variant of the pancreatobiliary type. Although IPNBs and IPMNs show many similarities, there are several remarkable differences. For example, IPMNs have a high percentage of adenoma or hyperplasia, whereas IPNBs have a significant percentage of cancer [6]. These biological features may affect the treatment plan. Recent studies have shown that the histologic phenotype of IPNB can affect clinical outcomes [6, 7]. If we make a general remark concerning IPMN of the pancreas, IPMNs of the pancreatobiliary and oncocytic types may have more malignant potential than those of the gastric and intestinal types [8–10]. In IPNB, recently, a multi-institutional, retrospective study of patients with mucinous cystic neoplasm of the liver or mucin-producing intraductal papillary neoplasm of the intrahepatic bile duct was published in Japan [11]. Oncocytic and gastric-type IPNB were associated with a favorable survival, while pancreatobiliary and intestinal-type IPNB had a poor survival. In our case, the distinct classification into four phenotypes may be difficult, but papillary lesion seems to be a pancreatobiliary type, according to the immunohistochemical examination. The spreading of IPNB generated from the cystic duct into extensive extrahepatic bile duct is recognized, while the gallbladder mucosa does not have any atypia, interestingly. IPNB is well recognized as a precancerous and early neoplastic lesion, and it has a better prognosis after surgical resection. Therefore; the way of our surgical procedure was considered to be both necessary and sufficient at this time. However, the different phenotypes of IPNB vary in morphologic futures and biological behavior, including their predisposition to invasion. Further molecular and pathological examination may certify a carcinogenesis pathway different from that of conventional bile duct carcinoma arising from flat dysplasia.

In conclusion, we herein reported a rare case of the spread of intraductal papillary neoplasm from the cystic duct of the biliary tree.

### Statement of Ethics

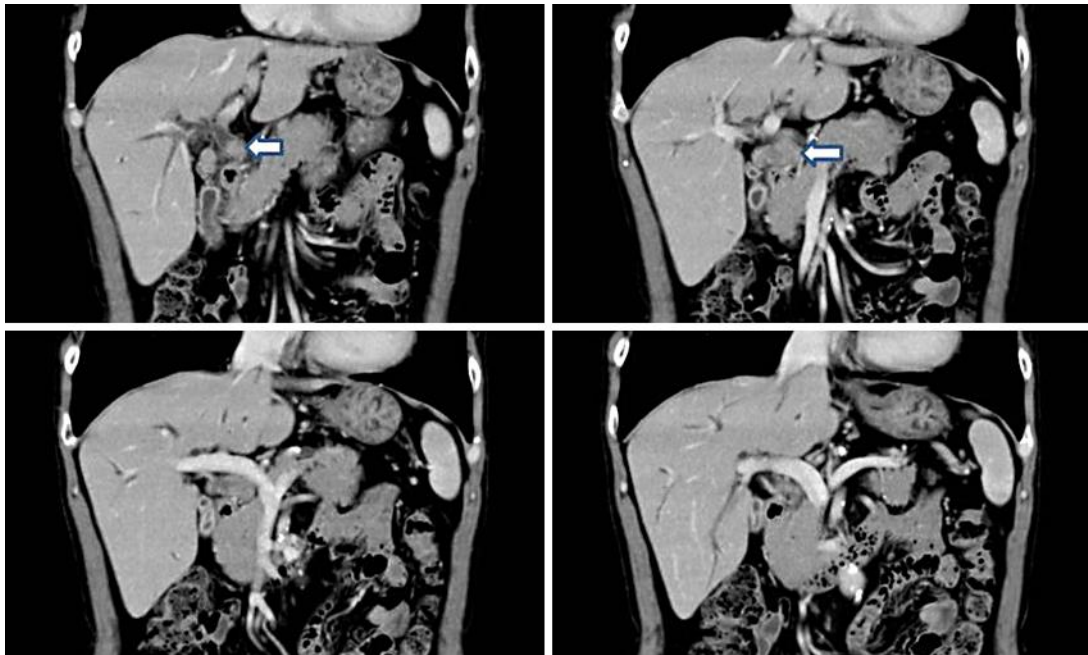
Consent was obtained from the patient for the publication of this case report.

### Disclosure Statement

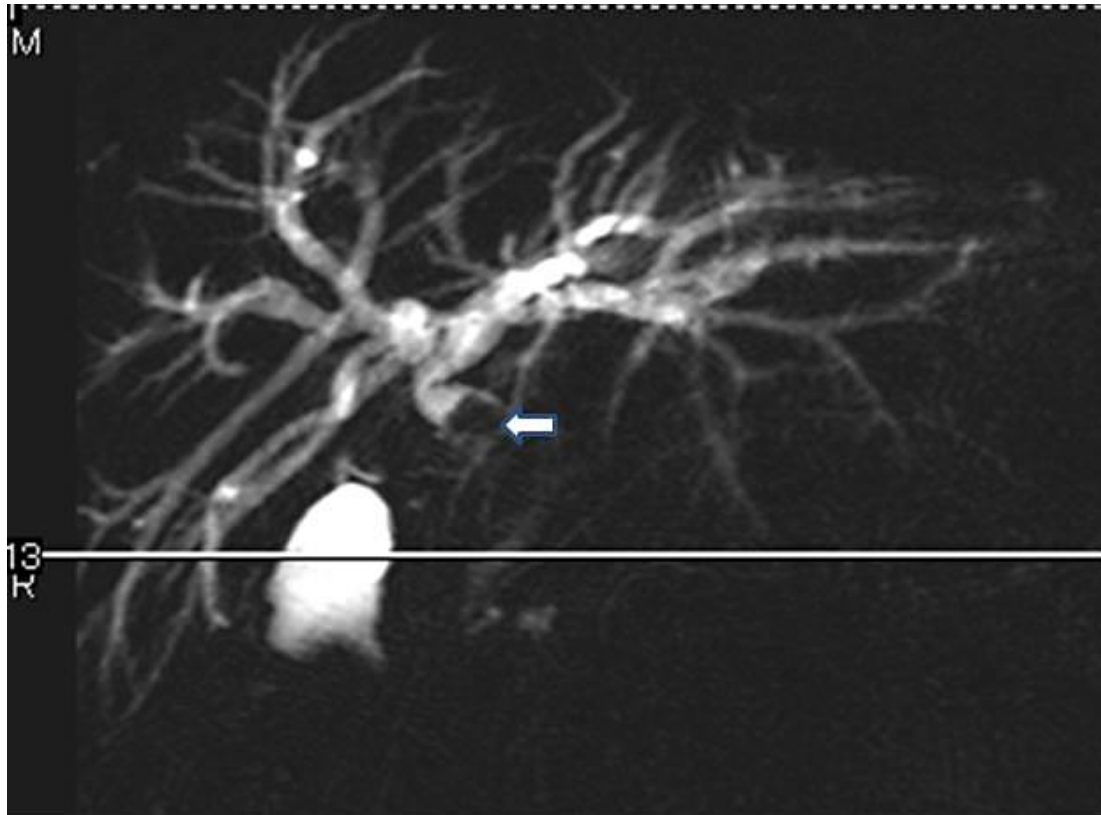
All authors declare no conflicts of interest.

### References

- 1 Nakanuma Y, Curabo MP, Franceschi S, et al: Intrahepatic cholangiocarcinoma; in Bosman FT, Carnerio F, Hruban RH, Theise ND (eds): WHO Classification of Tumours of the Digestive System, ed 4. IARC Press, Lyon, 2010, pp 217–224.
- 2 Zen Y, Fujii T, Itatsu K, Nakamura K, Minato H, Kasashima S, Kurumaya H, Katayanagi K, Kawashima A, Masuda S, Niwa H, Mitsui T, Asada Y, Miura S, Ohta T, Nakanuma Y: Biliary papillary tumors share pathological features with intraductal papillary mucinous neoplasm of the pancreas. *Hepatology* 2006;44:1333–1343.
- 3 Zen Y, Fujii T, Itatsu K, Nakamura K, Konishi F, Masuda S, Mitsui T, Asada Y, Miura S, Miyayama S, Uehara T, Katsuyama T, Ohta T, Minato H, Nakanuma Y: Biliary cystic tumors with bile duct communication: a cystic variant of intraductal papillary neoplasm of the bile duct. *Mod Pathol* 2006;19:1243–1254.
- 4 Chen TC, Nakanuma Y, Zen Y, Chen MF, Jan YY, Yeh TS, et al: Intraductal papillary neoplasia of the liver associated with hepatolithiasis. *Hepatology* 2001;34:651–658.
- 5 Nakanishi Y, Zen Y, Kondo S, Itoh T, Itatsu K, Nakanuma Y: Expression of cell cycle-related molecules in biliary premalignant lesions: biliary intraepithelial neoplasia and biliary intraductal papillary neoplasm. *Hum Pathol* 2008;39:1153–1161.
- 6 Kim KM, Lee JK, Shin JU, Lee KH, Lee KT, Sung JY, Jang KT, Heo JS, Choi SH, Choi DW, Lim JH: Clinicopathologic features of intraductal papillary neoplasm of the bile duct according to histologic subtype. *Am J Gastroenterol* 2012;107:118–125.
- 7 Ji Y, Fan J, Zhou J, Wang BS, Liu HB, Wu ZW, Tan YS: Intraductal papillary neoplasms of bile duct. A distinct entity like its counterpart in pancreas. *Histol Histopathol* 2008;23:41–50.
- 8 Takasu N, Kimura W, Moriya T, Hirai I, Takeshita A, Kamio Y, Nomura T: Intraductal papillary-mucinous neoplasms of the gastric and intestinal types may have less malignant potential than the pancreatobiliary type. *Pancreas* 2010;39:604–610.
- 9 Furukawa T, Hatori T, Fujita I, et al: Prognostic relevance of morphological types of intraductal papillary mucinous neoplasm of the pancreas. *Gut* 2011;60:509–516.
- 10 Adsay NV, Adair CF, Heffess CS, et al: Intraductal oncocytic papillary neoplasm of the pancreas. *Am J Surg Pathol* 1996;20:980–984.
- 11 Kubota K, Nakanuma Y, Kondo F, Hachiya H, Miyazaki M, Nagino M, Yamamoto M, Isayama H, Tabata M, Kinoshita H, Kamisawa T, Inui K: Clinicopathological features and prognosis of mucin-producing bile duct tumor and mucinous cystic tumor of the liver: a multi-institutional study by the Japan Biliary Association. *J Hepatobiliary Pancreat Sci* 2014;21:176–185.



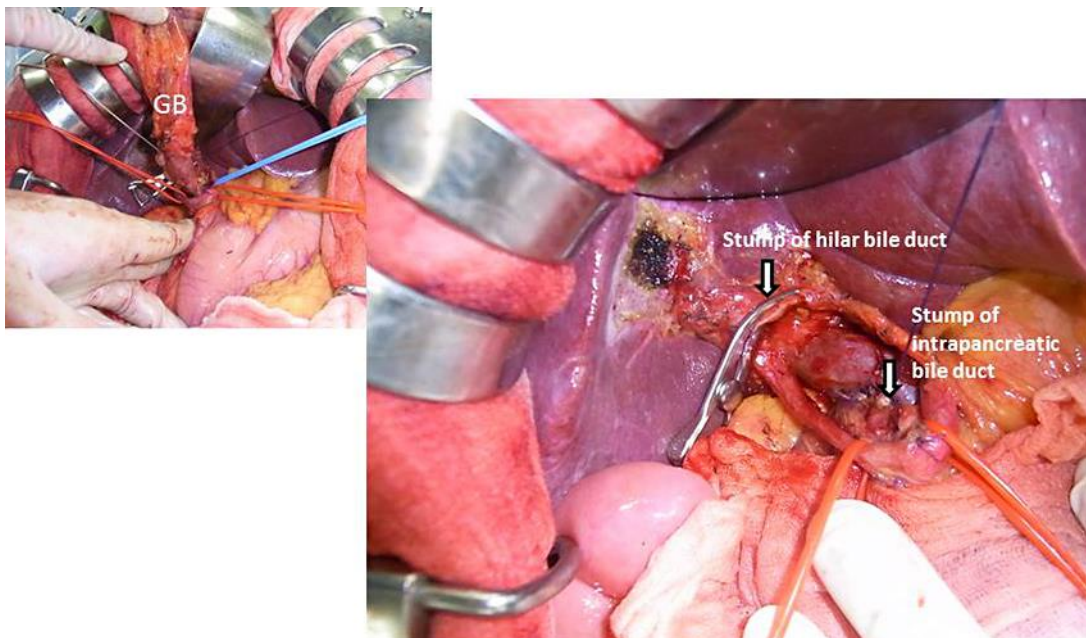
**Fig. 1.** Computed tomography scan of the abdomen showing a soft mass contiguously developed from the gallbladder neck to the upper-middle bile duct (arrows).



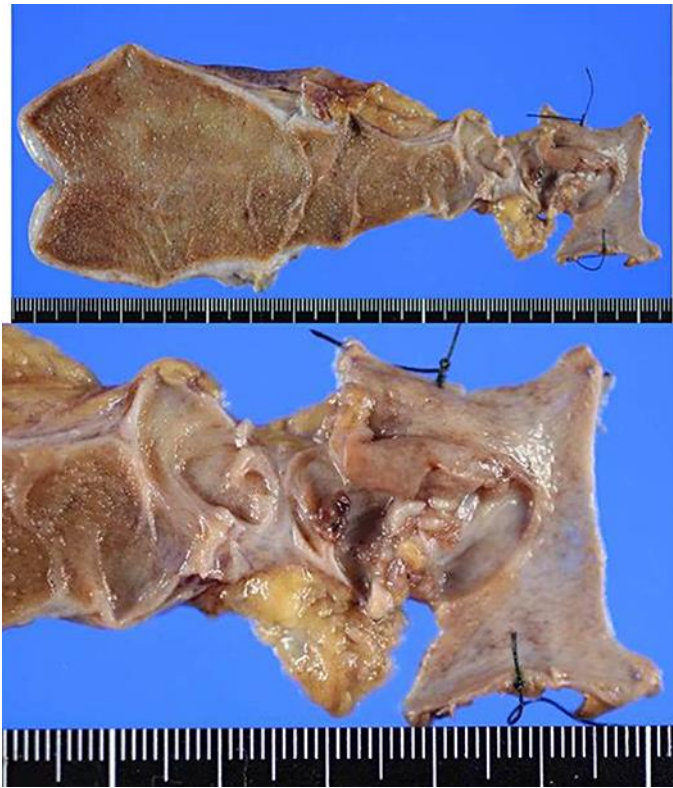
**Fig. 2.** Magnetic resonance cholangiopancreatography indicated diffuse dilation of the intrahepatic bile duct and the common hepatic duct. A tumor is seen in the bile duct (arrow).



**Fig. 3.** ERCP directly showed the mass spreading from the cystic duct to the upper-middle bile duct (arrows).

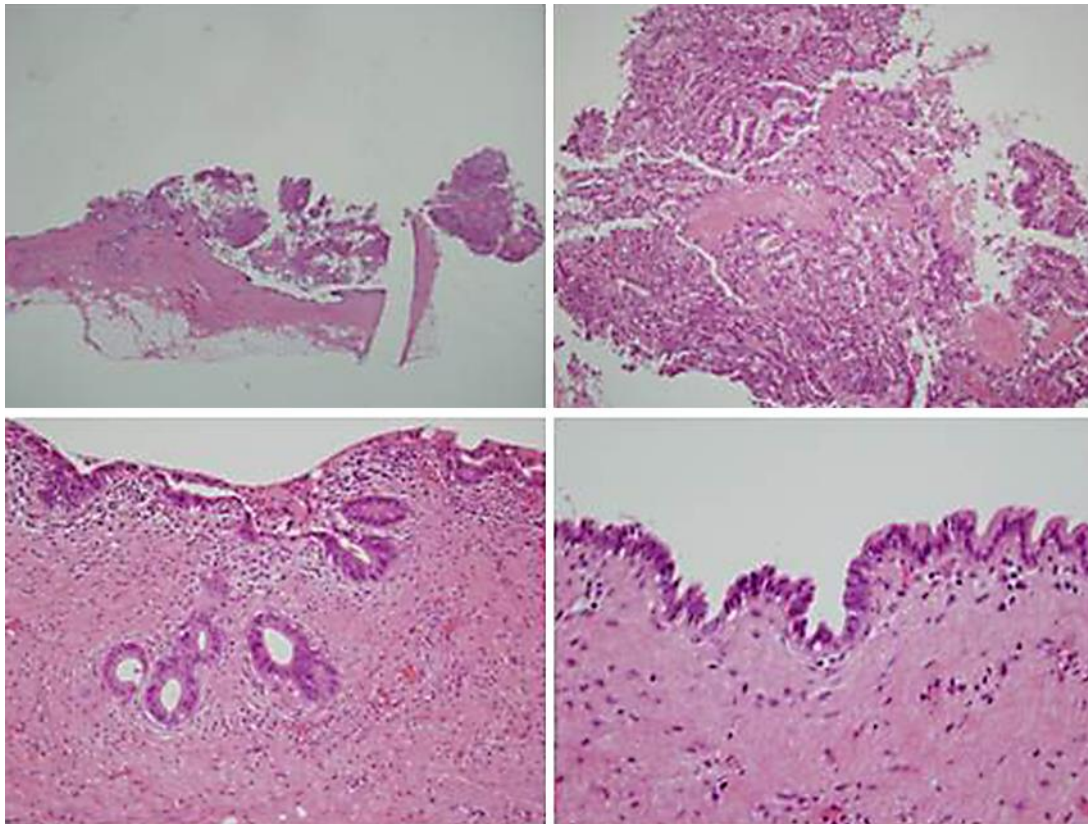


**Fig. 4.** Intraoperative picture after resection of the extrahepatic bile duct including the intrapancreatic bile duct.

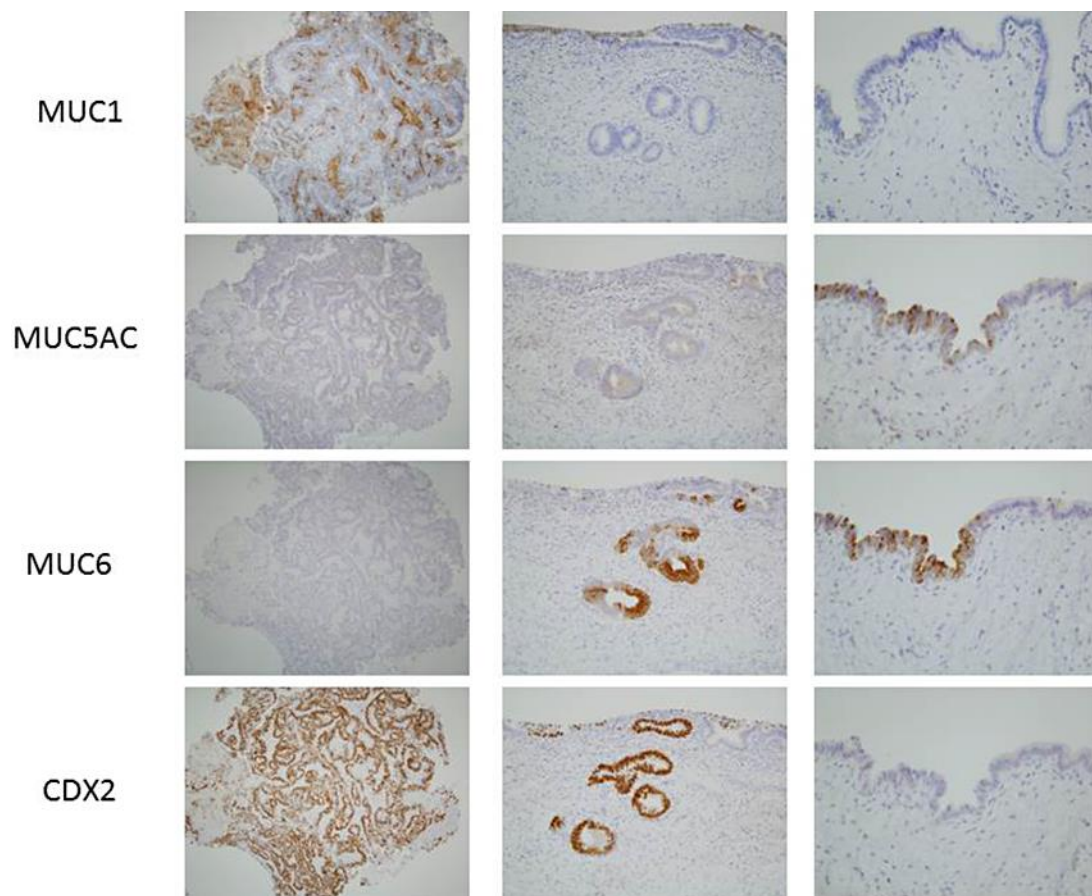


**Fig. 5.** Macroscopically, a papillary proliferated tumor is originated from the cystic duct.





**Fig. 6.** Histologic finding showed well-differentiated adenocarcinoma, which was superficially extending from the cystic duct to the epithelium of the whole extrahepatic bile duct. H&E.  $\times 40$ ,  $\times 100$ ,  $\times 200$ .



**Fig. 7.** Immunohistochemical examination revealed that MUC1 and CDX2 were positive but MUC2, MUC5AC and MUC6 were negative in the papillary region. MUC5AC and MUC6 were positive but MUC1, MUC2, and CDX2 were negative in the flat region.  $\times 200$ .