

Original Article

Non-invasive intraductal papillary neoplasms of the common bile duct: a clinicopathologic study of six cases

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Abstract: Recently, several studies of intraductal papillary neoplasms (IPN) of the biliary tracts have been reported in the liver, but there have been only one study of them in the common bile duct (CBD). The author reviewed 34 archival pathologic materials of surgically resected specimens containing CBD tumors. Results: Six cases (18%) of IPN of the CBD were found. All cases were non-invasive intraductal papillary carcinomas (IPC). The age of the patients with IPC ranged from 49 to 77 years with a mean of 67 years. The male to female ratio was 4:2. The initial symptoms were abdominal pain in 2 cases, abdominal discomfort in 1 case, and obstructive jaundice in 3 cases. Imaging modalities including US, CT, MRI, and ERCP revealed the CBD luminal tumors and biliary dilations in all cases. Surgical procedures were pancreaticoduodenectomy in 4 cases and segmental resection in 2 cases. The survival is relatively good; five patients are now alive, and one died of other disease. Grossly, all the 6 IPC showed intraductal papillary tumors. No mucus was found. Histologically, papillary proliferation of atypical cells with hyperchromatic nuclei regarded as malignant was recognized. The papillary proliferation was accompanied by fine fibrovascular cores in all cases. No stromal invasion was recognized, but lateral non-papillary in situ extension was recognized in 5 cases. Tubular formations were present in some areas in all cases. Goblet cells were present in 5 cases. No mucous hypersecretion was recognized. In one case, the tumor was composed of malignant oncocytes, and was regarded as intraductal oncocytic papillary carcinoma. Immunohistochemically, p53 expression was present in 5 cases, and Ki-67 labeling ranged from 30% to 70%. The author presented clinicopathologic findings of 6 cases of non-invasive IPC of the CBD.

Keywords: Common bile duct, intraductal papillary neoplasm, histopathology

Introduction

Intraductal papillary neoplasm of the pancreas and intraductal papillary-mucinous neoplasm of the pancreas are well established disease entities, and many studies of these pancreatic papillary neoplasms have been performed [1-11]. Recently, similar intraductal papillary neoplasms have been found in the intrahepatic biliary tree, and these intrahepatic biliary intraductal papillary neoplasms have been proposed as disease entities, i.e. intraductal papillary neoplasm and intraductal papillary-mucinous neoplasm [12-18]. Such intraductal papillary neoplasms of the intrahepatic biliary tree may correspond to biliary papillomatosis, a term used in the past [19]. Such biliary intraductal papillary neoplasms have been located in the intrahepatic bile ducts and frequently

associated with hepatolithiasis [12-18]. The author confirmed that previous reported biliary intraductal papillary neoplasms were really located within the intrahepatic bile ducts by extensive literature review. However, such intraductal papillary neoplasms have been described only once by Albores-Saavedra et al. [20] in the common bile duct, to the author's knowledge. They reported nine cases of non-invasive and minimally invasive papillary carcinomas of the extrahepatic bile ducts; seven in the common bile duct, one in the cystic duct, and one in the left hepatic duct [20]. The author herein reports the clinicopathologic features of six cases of non-invasive intraductal papillary neoplasm occurring in the common bile duct. In the present study, the term "intraductal papillary neoplasm" was defined as intraductal papillary tumor accompanied by fine fibrovascular

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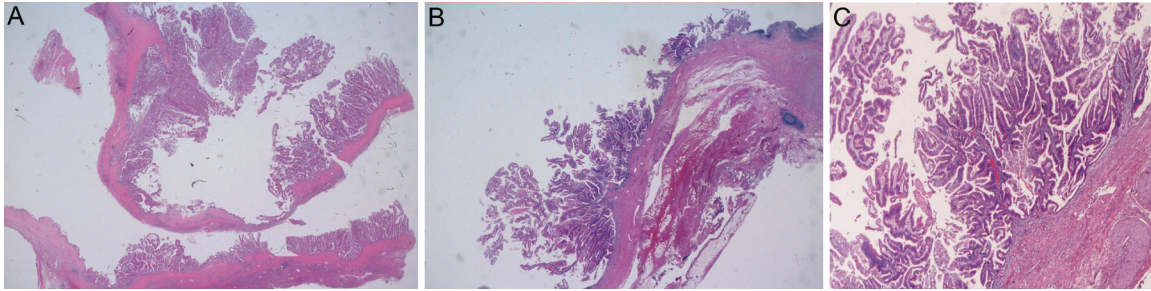


Figure 1. A: Very low power features of an intraductal papillary carcinoma of the common bile ducts. Two longitudinal sections of common bile duct are demonstrated. A malignant papillary proliferation with fine fibrovascular cores within the common bile duct is recognized. No invasion into the bile duct walls is noted, but lateral non-papillary in-situ spreadings were recognized. B: Very low power view of another intraductal papillary carcinoma of the common bile duct. Pathologic features are similar to A. C: Low power view highlights the pathologic features of A and B. HE, x10.

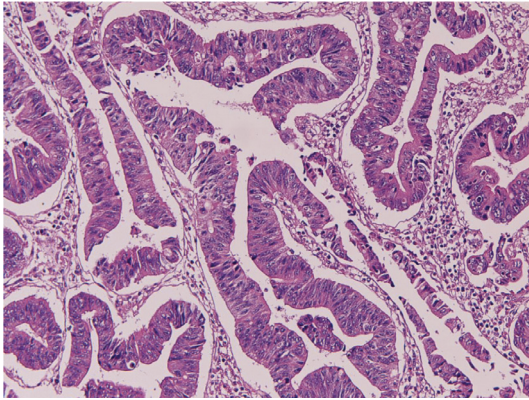


Figure 2. Higher power view of the lesion. There were papillo-tubular proliferations of malignant cells. HE, x200.

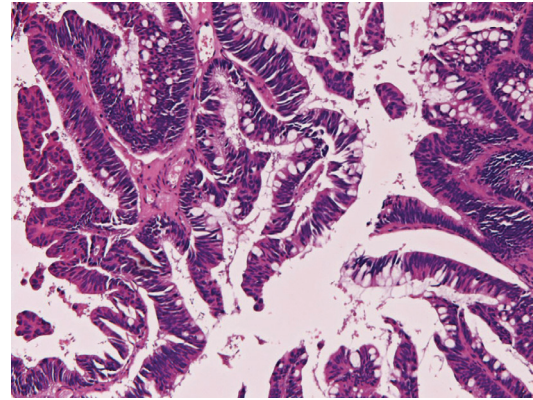


Figure 3. Malignant goblet cells are recognized. HE, x 200.

cores without mucus secretion, while the term “intraductal papillary-mucinous neoplasm” was defined as such intraductal papillary tumor with mucous hypersecretion. If there was no invasion into underlying bile duct walls, the tumor was defined as non-invasive.

Materials and methods

In the present study, the common bile duct was defined as an extrahepatic bile duct from the duct near the ampulla to the hepatic duct confluence. The common bile duct was further classified into intrapancreatic common bile duct, proximal common bile duct (proximal half of the non-intrapancreatic bile duct), and distal common bile duct (distal half of the non-intrapancreatic bile duct). Hepatic ducts, cystic duct, and ampullary duct were not included in the common bile duct. The criteria of malignan-

cy depended on structural atypia such as irregular papillae and tubules, stratification of nuclei, nuclear dipolarity, and piling up nuclei as well as on the cellular atypia such as hyperchromasia, mitotic figures, focal necrosis, and apoptotic figures. The presence of non-invasive, non-papillary, in situ carcinoma adjacent to the main intraductal papillary carcinoma was termed as “lateral spreading” in the present study.

The author reviewed 34 archival pathologic materials of surgically resected specimens containing the common bile duct tumors at our laboratory in the last 22 years, and found 6 cases (18%) of intraductal papillary neoplasms. Namely, 18% of common bile duct tumors were intraductal papillary neoplasms. There were no cases of intraductal papillary-mucinous neoplasm. All cases were non-inva-

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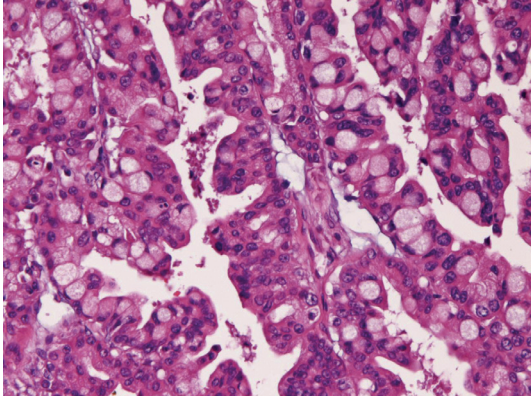


Figure 4. This tumor is composed of malignant oncocytic cells. HE, x200.

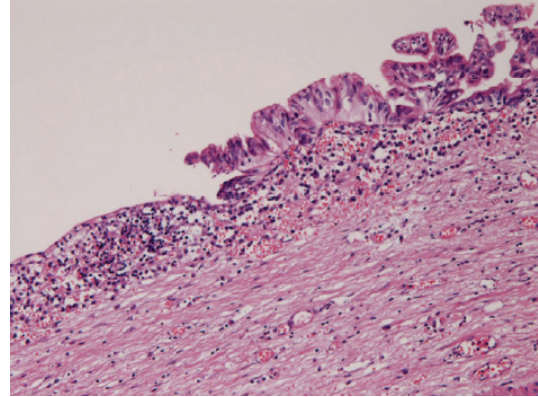


Figure 5. The lateral in situ spreading area shows non-invasive features of tumor cells with flat or micropapillary configurations. The biliary epithelial cells of the non-tumorous part (left) are desquamated. HE, x200.

sive intraductal papillary carcinomas. The original diagnoses of these 6 cases were intraductal papillary carcinoma in three cases, papillary adenocarcinoma in two cases, and well differentiated papillary carcinoma in one case. The remaining 28 cases did not show papillary structures, and were grossly non-papillary invasive carcinoma. The histology of these 28 cases were invasive well differentiated adenocarcinomas in 9 cases, invasive moderately differentiated adenocarcinomas in 12 cases, invasive poorly differentiated adenocarcinomas in 4 cases, invasive adenosquamous carcinomas in 2 cases, and invasive sarcomatoid carcinoma in one case. In situ elements of carcinoma were present in 5 cases among these 28 cases, but they were not papillary in configurations.

The clinical records were reviewed. The pathology was also reviewed. Of the 6 cases of intraductal papillary carcinoma of the common bile duct, frozen sections during operation had been performed to determine the surgical margins in 5 cases. In addition, an immunohistochemical study was performed by Dako's Envision method, as previously reported [21, 22]. The antigen examined were p53 protein (DO-7, Dako) and Ki-67 (MIB-1, Dako). In p53 evaluation, cases with p53 expression of more than 10% of tumor cells were labeled as positive. Ki-67 labeling was determined by counting positive cells in 1000 tumor cells in high power fields. Mucin stains are also performed.

Results

Clinical features

The age of the patients with intraductal papillary neoplasm of the common bile duct ranged from 49 to 77 years with a mean of 67 years. The male to female ratio was 4:2. The initial symptoms were abdominal pain in 2 cases, abdominal discomfort in 1 case, and jaundice in 3 cases. Imaging modalities including US, CT, MRI, and ERCP revealed the intraductal tumors and biliary dilations proximal to the tumors in all cases. The location of the intraductal papillary tumor was the intrapancreatic common bile duct in 1 case, the proximal common bile duct in 3 cases, and the distal common bile duct in 2 cases. Surgical procedures were pancreaticoduodenectomy in 4 cases and segmental resection in 2 cases. The survival was relatively good; five patients are now alive (survival periods: 110 months, 86 months, 76 months, 45 months, and 19 months) (mean \pm SD = 67 \pm 32 months), and one died of other disease (myocardial infarction, survival period = 54 months).

Pathologic features

Grossly, papillary tumors were present in 2 cases, and papillo-polypoid tumors were recognized in 4 cases. The size of the tumor ranged from 5mm to 20 mm. The three cases with

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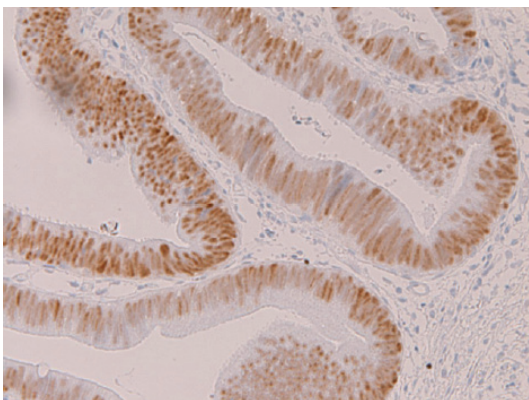


Figure 6. p53 protein expression is recognized. Immunostaining, x200.

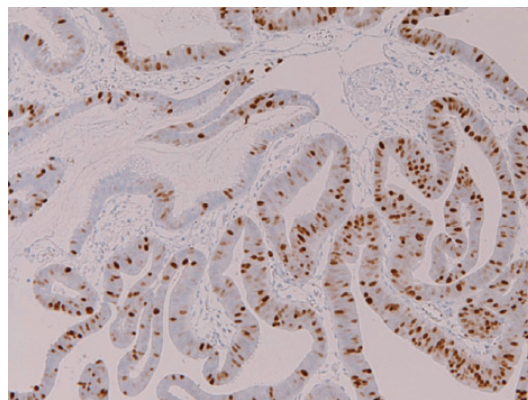


Figure 7. High Ki-67 labeling is recognized. Immunostaining, x200.

obstructive jaundice showed intraductal tumors obstructing the common bile duct. Bile duct dilations were noted proximal to the tumor in all cases. No mucus was present in the common bile duct lumina in all cases. No stone formation is noted in all cases.

Histologically, all the 6 intraductal tumors showed non-invasive intraductal papillary proliferation accompanied by fine fibrovascular cores (**Figures 1A, 1B and 1C**). Papillary proliferation of atypical cells with hyperchromatic nuclei regarded as malignant cells was recognized in all cases (**Figures 1C, 2, 3 and 4**). No stromal invasion was recognized in all cases (**Figure 1**). Lateral in situ mucosal spreading was recognized in 5 cases (**Figures 1 and 5**). The lateral spreading was almost always flat or micropapillary, in situ carcinomatous lesion (**Figure 5**). Tubular formations were present in some areas in all cases (**Figure 1 and 2**). Tumor goblet cells were present in 5 cases (**Figures 3 and 4**). Five cases showed histologically intestinal-type epithelium (**Figures 1, 2 and 3**). Non-invasive intraductal papillary carcinoma composed exclusively of oncocytic carcinoma cells was recognized in 1 case (**Figure 4**). Mucin stains including PAS, Alcian blue at pH 2.5 and 1.0, and combined Alcian blue at pH 2.5 and PAS showed a little neutral, sialylated and sulfated mucus in the tumor cytoplasm in all cases. The tumor goblet cells had abundant neutral, sialylated and sulfated mucus. No mucous hypersecretion was noted in all cases; mucins were absent in the extracellular spaces. Therefore, the present 6 cases are not intraductal papillary-mucinous neoplasms.

Immunohistochemically, p53 expression was present in the nuclei in 5 cases (**Figure 6**), the labeling of which was 8% (negative), 34%, 42%, 87% 92%, and 98% (mean \pm SD = 60 \pm 34 %). Ki-67 labeling was present in the nuclei, and it ranged from 30% to 70% (**Figure 7**) (labeling = 30%, 35%, 54%, 58%, 62%, and 70%) with a mean and SD of 52 \pm 14 %.

Discussion

Pancreatic intraductal papillary neoplasm is almost always accompanied by much mucous hypersecretion, so it is called intraductal papillary-mucinous neoplasm of the pancreas. It is classified into adenoma, borderline (dysplasia), and carcinoma in WHO classification [23]. It is characterized by much mucous hypersecretion. In contrast, biliary intraductal papillary neoplasm is usually not accompanied by much mucous hypersecretion [12-19]. However, Zen et al. [15] described that 28% (9/32) of intraductal papillary neoplasm of the intrahepatic bile ducts showed mucous hypersecretion, and proposed that the intraductal papillary neoplasm of the intrahepatic bile ducts are biliary counterpart of pancreatic intraductal papillary-mucinous neoplasm.

The present 6 cases showed no mucous secretion grossly and microscopically. Therefore, the present cases are different from intraductal papillary-mucinous neoplasm of the bile ducts, a suspected biliary counterpart of pancreatic intraductal papillary-mucinous neoplasm [1-11]. However, the entity of biliary intraductal papillary-mucinous tumors has not been

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established as yet. Albores-Saavedra et al. [20] reported 9 cases of non-invasive and minimally invasive papillary carcinomas of the extrahepatic bile duct; 7 in the common bile duct, 1 in the cystic duct, and 1 in the hepatic duct [20]. Their report of extrahepatic bile duct intraductal papillary carcinomas did not mention the mucous hypersecretion [20], being consistent with the present series.

Most of the reports of biliary intraductal papillary neoplasm or papillary-mucinous neoplasm are from Japan and China [12-16, 18], suggesting that these biliary neoplasms are prevalent in East Asia. In addition, most cases of such biliary neoplasms are located in intrahepatic bile ducts and are associated with hepatolithiasis, which is prevalent in Asia. The present study, no stone formation of the common bile duct was recognized, suggesting that the pathogenesis of the common bile duct intraductal papillary neoplasm is different from that of intraductal papillary neoplasm of the intrahepatic bile ducts.

Clinically, the symptoms of intraductal papillary neoplasm may be different depending on the location of the tumors. In the previous studies, the location of tumor is peripheral intrahepatic bile ducts. Therefore, the symptoms are non-specific such as abdominal pain and discomfort [17, 18]. In the present common bile duct tumors, the symptoms were abdominal pain in 2 cases, abdominal discomfort in 1 case, and obstructive jaundice in 3 cases. Obstructive jaundice is a characteristic sign and symptoms of common bile duct intraductal papillary neoplasms. The report of Albores-Saavedra et al. [20] stated that the symptoms of the intraductal papillary neoplasm of the common bile duct were similar to those of ordinary extrahepatic bile duct carcinomas. The age of the patients reported previously is around 60 years, being not different from the present common bile duct tumors. Male predominated over female in the previous studies [17, 18] and in the present study. The age of the patients of the report of Albores-Saavedra et al. [20] ranged from 48 to 83 years with a mean of 65 years, and the patients consisted of 6

male and 3 female. Imaging modalities of previous studies showed biliary dilation or cyst, and tumor formation [18]. The present study also showed biliary dilation and intraductal tumors. The best treatment of the tumor is surgical resection [18, 20]. The previous studies of intrahepatic papillary neoplasms showed that hepatectomy is the best choice [17, 18]. In the present cases of common bile duct tumors, pancreaticoduodenectomy was performed with good results. The prognosis is good in operation cases in previous studies [18]. The present common bile duct tumors showed relatively good prognosis. Albores-Saavedra et al. [20] also described relatively good prognosis after surgery in the common bile duct intraductal papillary carcinomas.

Pathologically, all the intraductal papillary neoplasms in the present series were malignant, i.e. intraductal papillary carcinoma, and were non-invasive. The 7 cases of Albores-Saavedra et al. [20] were also intraductal papillary carcinomas of the common bile duct. In previous series, benign intraductal papillary neoplasms have been reported in the liver [12-18]. The present series suggest that most of the intraductal papillary neoplasms in the common bile duct are malignant intraductal papillary carcinoma, similar to the report of Albores-Saavedra et al. [20]. The present intraductal papillary carcinomas showed no stromal invasion but indicated lateral in situ spreading. The latter was already described in hepatic intraductal papillary neoplasm [12-18]. The "lateral spreading" may be tumor cells' in situ invasion, but it may be early flat or micropapillary malignant transformation of the common bile duct. The lateral spreading is important in determining the surgical cut margins during operation; surgical margin check by frozen sections during the operation is mandatory.

The present series showed goblet cells and intestinal-type epithelium in 5 cases. Albores-Saavedra et al. [20] described that their 9 extrahepatic intraductal papillary carcinomas of the common bile duct were composed of 7 biliary type tumors and 2 intestinal tumors. A previous study revealed that CDX2 expression is associated with tumor goblet cells in hepatic intraductal papillary neoplasms [12]. Although the present series did not examine CDX2 and MUC apomucins, the present intraductal papil-

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lary neoplasms of the common bile duct belong to intestinal type intraductal papillary neoplasm [11]. More study of MUC apomucins and CDX2 expressions are required in common bile duct intraductal papillary neoplasms.

It was of particular interest that one case of the present series was composed of malignant oncocytes. This case was an intraductal oncocytic papillary neoplasm, as reported in the intrahepatic bile duct [24], extrahepatic bile duct [25], and pancreas [7]. Further studies of this variant of intraductal neoplasm of the common bile duct are required.

The author thinks that the non-invasive intraductal papillary carcinoma in the present series is a disease entity, but it may be a condition of a spectrum of papillary carcinoma. Microinvasive papillary carcinoma [20] and invasive papillary carcinoma of the common bile duct [26-28] were reported. These papillary neoplasms share common clinical and pathologic features. Clinically, the prognosis is relatively good prognosis, and pathologically they show papillary carcinoma with fibrovascular cores [20, 26-28]. It seems possible that the non-invasive intraductal papillary carcinoma become microinvasive and finally give rise to invasive papillary carcinoma of the common bile duct.

The non-invasive intraductal papillary carcinoma of the present study should be differentiated from several papillary lesions of the common bile duct, including biliary papillomatosis, papillary and villous adenomas, primary papillary hyperplasia, and biliary extension of pancreatic intraductal papillary mucinous neoplasms [20]. Biliary papillomatosis is a benign condition characterized by multiple recurring papillary adenomas that involve broad areas of the biliary tracts [19, 28]. Papillary and villous adenomas are benign condition with features of intestinal or biliary types [28]. Primary papillary hyperplasia is also a benign condition without atypia [20, 28]. The present cases are non-invasive carcinomas, and are different from these conditions. In addition, the present cases are different from biliary extension of pancreatic intraductal papillary-mucinous neoplasm, because the present cases show no evidence of pancreatic neoplasms.

The present series showed that p53 expression was present in 5 cases. Albores-Saavedra et al. [20] also mentioned that intraductal papillary carcinomas of the common bile duct were positive for p53 and Ki-67. One previous report showed that p53 expression was almost absent in hepatic intraductal papillary neoplasms [14]. This difference may be due to the tumor locations and tumor malignant potential. The present series were carcinoma in all cases, so that p53 expression is not peculiar. In the present series, the Ki-67 labeling ranged from 30 to 70%, suggesting a high proliferative activity of the present tumors. The p53 expression and high Ki-67 labeling highly suggest that the present tumors are malignant.

In summary, the author presented clinicopathologic findings of 6 cases of non-invasive intraductal papillary carcinoma of the common bile duct, a rare condition. This study is the second report, next to that of Albores-Saavedra et al. [20], of intraductal papillary carcinoma of the common bile duct.

Conflict of interest statement

The author has no conflict of interest

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