

CASE REPORT

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Intraductal papillary neoplasm of extrahepatic biliary tract with an associated early invasive adenocarcinoma

Jayathilaka Karunanayake Hiroshi, Siriwardhana Rohan, Nawaratne NMM, Mahendra Gayana, Liyanage Chandika

ABSTRACT

Introduction: Intraductal papillary neoplasm of the bile duct is a premalignant lesion, which can develop into an adenocarcinoma. If treated early, at the non-invasive stage, it has an excellent prognosis compared to cholangiocarcinoma. **Case Report:** A 61-year-old female presented with intermittent episodes of fever with chills and rigors, loss of appetite, pruritus, tea colored urine, and pale sticky stools for two years duration. After work up she underwent a left hemihepatectomy with resection of caudate lobe and extrahepatic biliary duct with lymph node clearance. Histology revealed an intraductal papillary lesion with no mucin production, expanding the common hepatic duct and the left hepatic duct, invading the subepithelial connective tissue at a focus near the distal end of the left hepatic duct. The tumor was qualified as an intraductal papillary neoplasia of pancreatobiliary type involving the extrahepatic bile duct with associated early

invasive adenocarcinoma. She required no further adjuvant treatment and is disease free for one year on regular follow-up. **Conclusion:** The objective of this article is to emphasize the necessity of early diagnosis and aggressive and complete surgical resection to achieve maximum patient survival in this curable disease.

Keywords: Extra hepatic intraductal papillary neoplasm, Biliary papillomatosis, Biliary pre malignant lesion

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INTRODUCTION

Intraductal papillary neoplasm of the biliary tract (IPNB) is considered a precursor lesion for the development and progression of both intrahepatic and extrahepatic bile duct adenocarcinoma. These papillary neoplasms are characterized by dilated and expanded bile ducts filled with a non-invasive papillary growth. The papillae are composed of proliferating biliary epithelium covering delicate fibro vascular stalks. Four phenotypes of epithelium are recognized which include pancreaticobiliary, intestinal, oncocytic, and gastric types. Invasive adenocarcinoma may occur in association

with intraductal papillary neoplasms. The prognosis is excellent if an IPNB is localized and non-invasive, in which case the tumor can be completely resected. Once invasive carcinoma develops the prognosis becomes remarkably poor [1].

The available literature on this rare neoplasm is limited. Therefore, the clinical course, radiological and pathologic findings, and prognosis of this neoplasm are not well understood. Although the frequencies of reports are increasing, data from South Asian context is sparse. We report a case of intraductal papillary neoplasm of extra hepatic biliary tract with evidence of an associated early invasive adenocarcinoma to emphasize the importance of precise diagnosis at an early stage and early surgical resection.

CASE REPORT

A 61-year-old female presented to the primary care clinic with episodes of epigastric pain radiating to the back for two years duration. She has had episodes of fever with chills and rigors, loss of appetite, pruritus, tea colored urine, and pale sticky stools. These episodes developed at least once in every three months. She never had jaundice in association with these symptoms. The ultrasound scan of the abdomen revealed dilated intrahepatic ducts with no visible calculi. The patient was referred to specialized hepatobiliary clinic for further management.

The contrast-enhanced computed tomography (CECT) scan of the abdomen was done and it was more in favor of an intraductal cholangiocarcinoma involving left and right hepatic ducts, common hepatic duct and proximal segment of common bile duct (Bismuth type IV) with regional nodal metastasis. A magnetic resonance cholangiopancreatography (MRCP) delineated a mildly enhancing soft tissue mass involving the proximal right and left hepatic ducts, common hepatic duct and proximal common suprapancreatic biliary duct causing mild dilatation of the bilateral intrahepatic biliary radicles suggestive of cholangiocarcinoma with a normal liver. (Figure 1)

The laboratory test results showed; CA 19.9 13.4 u/mL (0–5 u/mL), AST 86 IU/L (10–35 IU/L), ALT 88 IU/L (10–40 IU/L), ALP 2043 IU/L (100–360 IU/L), total bilirubin 3.6 mg/dL (<1 mg/dL), serum creatinine 0.6 mg/dL (0.9–1.3 mg/dL), sr amylase 270 U/L (30–110 U/L), hemoglobin 11.2 g/dL (11–18 g/dL), white blood cell $8 \times 10^3/\text{mm}^3$ ($4.5\text{--}10.5 \times 10^3/\text{mm}^3$)

The clinical details and the investigations were discussed at the Hepatobiliary multi-disciplinary team (MDT) meeting. A 10Fr \times 12 cm end biliary stent was placed following endoscopic retrograde cholangiopancreatography (ERCP). Patient had four cycles of radiofrequency ablations (RFA) as the lesion was deemed unresectable on CT scan and MRCP. One month later the previous sphincterotomy was extended and a cholangioscopy was performed to assess the progression

of the disease and the effect of radiofrequency ablations. Cholangioscopy and biopsy from the mass was non-diagnostic and yielded fibrous stromal tissue only. As the symptoms recurred, a repeat ERCP was performed and it revealed sparing of right hepatic duct (Bismuth 111b). Right hepatic artery and right branch of the portal vein were assessed by a CT angiogram/venogram and were found not to be involved. Patient was re-evaluated at the MDT and was offered surgery to exclude a hilar cholangiocarcinoma. The patient underwent left hemihepatectomy with resection of caudate lobe and extrahepatic biliary duct with lymph node clearance. A Roux-en-Y hepaticojejunostomy was performed to reconstruct the right hepatic duct. The patient had an uneventful recovery and was discharged on the seventh postoperative day.

The resected specimen consisted of left lobe of the liver, gall bladder and extrahepatic biliary tree including left hepatic duct, common hepatic duct, cystic duct and proximal common bile duct. On cutting open biliary duct system revealed no definite growth but only a mucosal irregularity. The gall bladder and the liver tissue were unremarkable with no evidence of lithiasis.

The entire extrahepatic biliary tree was examined microscopically and this showed a multifocal intraductal papillary lesion, expanding the left hepatic duct and the common hepatic duct. It was composed of arborizing papillae lined by moderately pleomorphic cells of pancreaticobiliary differentiation (Figures 2, 3). There was no mucin production. This intraductal tumor was invading the subepithelial connective tissue at a focus near the distal end of left hepatic duct (Figure 4). The invasive component was composed of irregular acinar structures infiltrating through the desmoplastic stroma. No perineural or vascular invasion was identified. No intrahepatic ductal component was identified. The hepatic parenchyma showed mild to moderate steatosis. The portal tracts showed extensive bile ductular reaction and moderate inflammatory infiltrate in keeping with the morphological changes of large bile duct obstruction. The gall bladder showed no lithiasis or epithelial dysplasia. Thus this tumor was qualified as an intraductal papillary neoplasm associated with early invasive adenocarcinoma-pancreaticobiliary type (PT_{1a}N₀M_x).

The patient did not receive further adjuvant treatment but was enrolled for follow up which is planned at regular intervals via clinical examination and biochemical investigations (liver profile. CA 19.9). Radiological investigations will be considered if a need arises.

DISCUSSION

Premalignant biliary and pancreatic lesions are rare disorders [2]. The recent WHO classification of tumors of the gall bladder and extrahepatic bile ducts proposed two precursor lesions for the development and progression of extrahepatic biliary carcinoma namely biliary

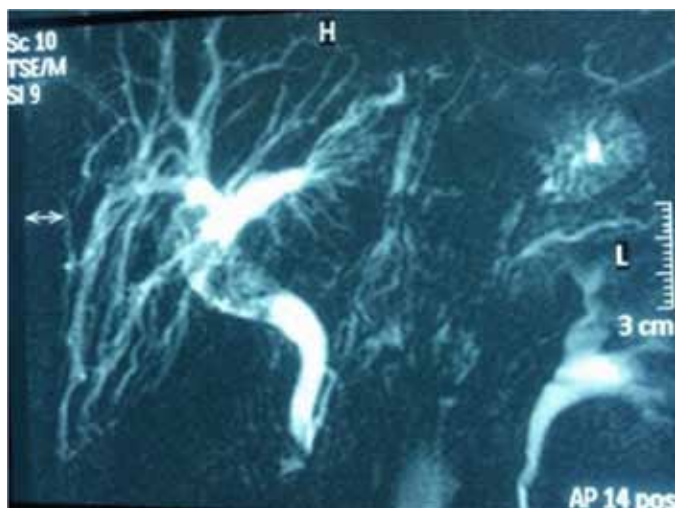


Figure 1: Magnetic resonance cholangiopancreatography (MRCP) showing a mildly enhancing soft tissue mass involving the proximal right and left hepatic ducts, common hepatic duct and proximal common suprapancreatic bile duct causing mild dilatation of the bilateral intrahepatic biliary radicles.

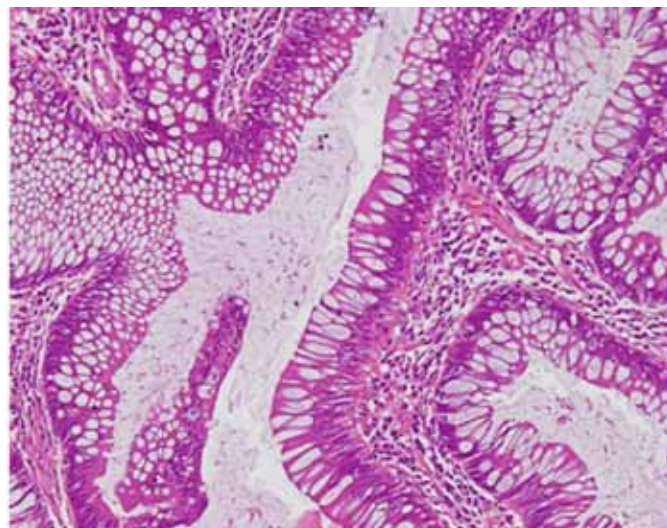


Figure 3: The papillae were lined by tall columnar cells that resemble pancreatic biliary type epithelium. The nuclei show moderate pleomorphism. (H&E stain, x200)

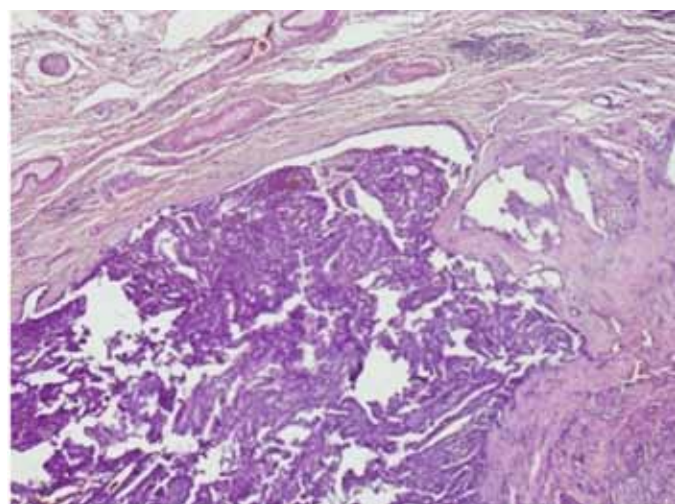


Figure 2: Intra ductal complex papillary lesion within the left hepatic duct. (H&E stain, x400)

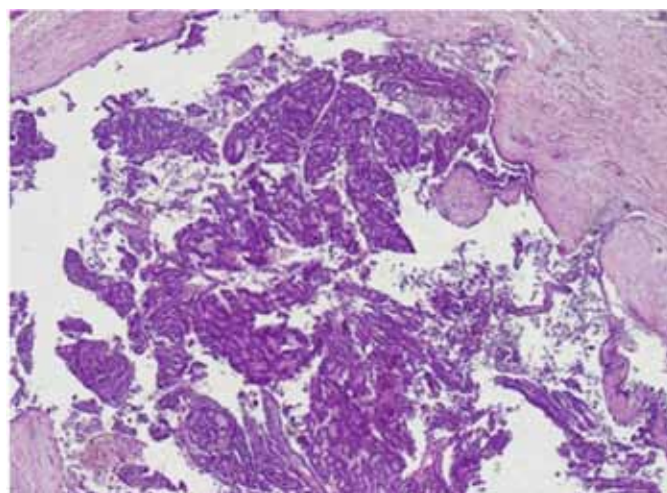


Figure 4: The intraductal tumor invaded the subepithelial connective tissue in a focus near the origin of the left hepatic duct. (H&E stain, x200)

intraepithelial neoplasia (BilIN) and intraductal papillary neoplasm (IPNB) [1].

Intraductal papillary neoplasm of the biliary tract is the clinicopathological condition which was previously referred to as biliary papillomatosis [1]. It is characterized by intraductal papillary proliferation of atypical biliary epithelium over a delicate fibrovascular stalk that may involve extensive areas of extrahepatic bile ducts and even extend into the gallbladder and intrahepatic bile ducts. Four phenotypes of epithelium are recognized and include pancreaticobiliary type which is the most common type of epithelium identified in IPNB; intestinal, oncocytic and gastric types. The lining cells are cuboidal or columnar and may contain variable amount of cytoplasmic and extracellular mucin. The nuclei are round, ovoid or elongated and contains small nucleoli [3].

Cytological atypia and mitoses are uncommon although obvious carcinomatous changes can be identified in some cases [4, 5].

Despite its rarity IPNB/biliary papillomatosis has been extensively discussed in the literature because of its characteristic clinical presentation and proven malignant potential [4]. These intraductal tumors with frond like papillary projections are friable and slough easily giving rise to fragments of floating tumor within the bile ducts. This could give rise to intermittent and partial biliary obstruction and clinically and radiologically mimic biliary stone disease. [6, 7]. Our patient had episodic symptoms of acute cholangitis and biliary obstruction for two years which would be most likely due to intermittent sloughing off of the tumor into the duct system.

In the previous edition of WHO classification of tumors of the gallbladder and extrahepatic bile ducts, biliary papillomatosis was considered a benign entity with a variable malignant potential [8]. The current edition includes papillomatosis under the novel entity of IPNB and classifies it as a premalignant lesion [1]. Intraductal papillary neoplasm of the biliary tract could have low, intermediate or high grade intraepithelial neoplasia. Some of these intraductal papillary lesions could invade beyond the wall of the bile duct to cause an invasive carcinoma as in our patient. Once invasive carcinoma develops prognosis is related to the stage of the invasive component and other conventional prognostic factors. The prognosis is excellent if an IPNB is localized and non-invasive, in which case the tumor can be completely resected. Wide distribution and invasion raises the potential for metastasis, causes surgical eradication difficult and hence a poor prognosis. Perineural invasion and lymphatic permeation are common and are significant prognostic indicators [1].

Intraductal papillary neoplasm of the biliary tract may evolve through a common pathological process and shares clinico-pathological features with pancreatic neoplasms such as intraductal papillary mucinous neoplasm of the pancreas (IPMN-P) [9, 10]. It is well established that intraepithelial pancreatic neoplasia is the microscopic precursor of pancreatic carcinoma and IPMN-P, and mucinous cystic neoplasms are the macroscopic precursor lesions [11, 12]. In bile duct carcinoma on the other hand BilIN or IPNB are thought to be similar precursor lesions and molecular characteristics of these in regard to carcinogenesis have been clarified [13]. Therefore, IPNB seems to be a counterpart of IPMN-P. Occasional association with mucin hypersecretion is one of the histological similarities between IPNB and IPMN-P, although the degree of extracellular mucin production may not always be as extensive as that found in most pancreatic IPMN [14]. A study done by Ohtsuka et al. concluded that IPNB with mucin secretion showed striking similarities to IPMNP, but IPNB without mucin secretion contained a heterogeneous disease group [15].

Terada T. [16] presented six cases and Albores-Saavedra et al. [17] reported nine cases of non-invasive and minimally invasive papillary carcinoma of the extrahepatic bile duct. Their cases of intraductal papillary carcinoma of extrahepatic bile duct did not show macroscopic and microscopic mucous hypersecretion [16, 17], as seen in this case. Therefore, the above group can be considered different from intraductal papillary-mucinous neoplasm of the bile ducts, a suspected biliary counterpart of pancreatic intraductal papillary-mucinous neoplasm [18, 19].

Though early detection and early treatment are important in the treatment of bile duct cancer, it is necessary to subclassify it according to the clinico-pathological characteristics. Based on morphology of the cells forming the lesion they are subdivided into pancreatobiliary, intestinal, gastric, or oncocytic [20].

Intraductal papillary neoplasm of biliary track (IPNB) can be also classified morphologically into polypoid, cast-like growth, superficial-spreading and cystic type [21]. However, no correlation has been demonstrated between these features and the tendency for invasive cholangiocarcinoma or survival rates [1, 22–24].

A study done in 2008 pointed out that 20% of IPNB were incidentally identified [25]. This disease has equal distribution among males and females. The most common age group affected is between 50–70 years [1].

Use of CT scan for revealing intraductal lesions has been found to be nonspecific and variable. Computed tomographic scan in 92% cases showed bile ducts dilatation with or without an intraductal mass and cystic change of bile duct [25]. When intraductal masses or nodules are seen with localized dilatation of the intrahepatic bile duct on CT scan, malignant papillary tumor of the intrahepatic bile duct should be included in the differential diagnosis [24].

The treatment of choice for IPNB is aggressive surgical resection [25]. But there are a few rare reported cases of IPNB, managed long-term using endoscopic procedures such as endoscopic retrograde biliary drainage, endoscopic biliary sphincterotomy and papillary balloon dilatation [26]. According to Yeh et al. 59 out of 129 (46%) cases of IPNB cases had progressed to invasive carcinoma at the time of diagnosis [27]. As this can be considered relatively a high proportion, the need for early diagnosis and excision is recommended. Once invasive carcinoma develops, prognosis is related to the stage of the invasive component and other conventional prognostic factors [1]. Some of the reports have revealed a very poor prognosis in patients with lymph node metastasis [27]. In addition, several reports have suggested excellent prognosis with minimal recurrence rate of IPNB over cholangiocarcinoma [15, 16, 25]. One study has indicated the median survival time of resected patients as 59.8 months and 1-, 2-, and 4-year survival rates as 90.5%, 84.0%, and 84.0%, respectively [25].

Considering the above factors as well as the difficulty of surgical excision in the hilar region and aggressive behavior of widely distributed disease, the possibility of early surgical resection with the curative intent should always be sought.

In this case the major component of the lesion is the intraductal papillary neoplasm, which is considered a pre-malignant lesion with good prognosis. However, as there is a focus of invasion qualifying this tumor as intraductal papillary neoplasm with associated adenocarcinoma the prognosis is worse than that of a pure intraductal lesion.

CONCLUSION

Considering the malignant potential of intraductal papillary neoplasm of biliary track (IPNB) which was well demonstrated in this case and the poor prognosis of hilar cholangiocarcinomas these premalignant lesions merits

early diagnosis and complete surgical resection to obtain best prognostic benefits.

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Author Contributions

Karunanayake Hiroshi Jayathilake – Conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Critical revision of the article, Final approval of the version to be published

Rohan Siriwardhane – Analysis and interpretation of data, Drafting the article, Critical revision of the article, Final approval of the version to be published

NMM Nawarathne – Conception and design, Analysis and interpretation of data, Critical revision of the article, Final approval of the version to be published

Gayana Mahendra – Analysis and interpretation of data, Drafting the article, Critical revision of the article, Final approval of the version to be published

Chandika Liyanage – Conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Critical revision of the article, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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REFERENCES

1. Bosman FT, Carneiro F, Hruban RH, Theise ND. Tumours of the gall bladder and extrahepatic bile ducts. In WHO Classification of tumors. 4th edition IARC press 2012:263–78.
2. Friess H, Holzinger F, Liao Q, Büchler MW. Surveillance of pre-malignant disease of the pancreato-biliary system. *Best Pract Res Clin Gastroenterol* 2001 Apr;15(2):285–300.
3. Albores-Saavedra J, Henson DE, Klimstra DS, Albores-Saavedra J, Henson DE, Klimstra DS. Tumors of the gallbladder, extrahepatic bile ducts and ampulla of Vater. Fascicle 24. Washington, DC: Armed Forces Institute of Pathology 2000:1–60.
4. Vassiliou I, Kairi-Vassilatou E, Marinis A, Theodosopoulos T, Arkadopoulos N, Smyrniotis V. Malignant potential of intrahepatic biliary papillomatosis: A case report and review of literature. *World J Surg Oncol* 2006 Oct 7;4:71.
5. Neumann RD, LiVolsi VA, Rosenthal NS, Burrell M, Ball TJ. Adenocarcinoma in biliary papillomatosis. *Gastroenterology* 1976 May;70(5 PT.1):779–82.
6. Nanashima A, Sumida Y, Tomoshige K, et al. A case of intraductal papillary neoplasm of the bile duct with stromal invasion. *Case Rep Gastroenterol* 2008 Sep 30;2(3):314–20.
7. Lim JH, Kim MH, Kim TK, et al. Papillary neoplasm of the bile duct that mimic biliary stone disease. *Radiographics* 2003 Mar-Apr;23(2):447–55.
8. Hamilton SR, Aaltonen LA. Tumours of the gallbladder and extrahepatic bile ducts, Pathology and genetics of tumours of the digestive system, IARC press 2000:203–17.
9. Zen Y, Fujii T, Itatsu K, et al. Biliary papillary tumors share pathological features with intraductal papillary mucinous neoplasm of the pancreas. *Hepatology* 2006 Nov;44(5):1333–43.
10. Nakanuma Y. A novel approach to biliary tract pathology based on similarities to pancreatic counterparts: Is the biliary tract an incomplete pancreas? *Pathol Int* 2010 Jun;60(6):419–29.
11. Sohn TA, Yeo CJ, Cameron JL, Iacobuzio-Donahue CA, Hruban RH, Lillmoie KD. Intraductal papillary mucinous neoplasms of the pancreas: An increasingly recognized clinicopathologic entity. *Ann Surg* 2001 Sep;234(3):313–21.
12. Yonezawa S, Higashi M, Yamada N, Goto M. Precursor lesions of pancreatic cancer. *Gut Liver* 2008 Dec;2(3):137–54.
13. Bickenbach K, Galka E, Roggin KK. Molecular mechanisms of cholangiocarcinogenesis: are biliary intraepithelial neoplasia and intraductal papillary neoplasms of the bile duct precursors to cholangiocarcinoma? *Surgical Oncology Clinics of North America* 2009 Apr;18(2):215–24.
14. Abraham SC, Lee JH, Boitnott JK, Argani P, Furth EE, Wu TT. Microsatellite instability in intraductal papillary neoplasms of the biliary tract. *Mod Pathol* 2002 Dec;15(12):1309–17.
15. Ohtsuka M, Kimura F, Shimizu H, et al. Similarities and differences between intraductal papillary tumors of the bile duct with and without macroscopically visible mucin secretion. *Am J Surg Pathol* 2011 Apr;35(4):512–21.
16. Tadashi Terada. Non-invasive intraductal papillary neoplasms of the common bile duct: A clinicopathologic study of six cases. *Int J Clin Exp Pathol* 2012;5(7):690–7.
17. Albores-Saavedra J, Murakata L, Krueger JE, Henson DE. Noninvasive and minimally invasive papillary carcinomas of the extrahepatic bile ducts. *Cancer* 2000 Aug 1;89(3):508–15.
18. Terada T, Ohta T, Kitamura Y, Ashida K, Matsunaga Y. Cell proliferative activity in intraductal papillary-mucinous neoplasms and invasive ductal adenocarcinomas of the pancreas: An immunohistochemical study. *Arch Pathol Lab Med* 1998;122(1):42–6.

19. Adsay NV, Adair CF, Heffes CS, Klimstra DS. Intraductal oncocytic papillary neoplasm of the pancreas. *Am J Surg Pathol* 1996;20(8):980–94.
20. Kim H, Lim JH, Jang KT, et al. Morphology of intraductal papillary neoplasm of the bile ducts: Radiologic-pathologic correlation. *Abdom Imaging* 2011 Aug;36(4):438–6.
21. Yaman B, Nart D, Yilmaz F, Coker A, Zeytunlu M, Kilic M. Biliary intraductal papillary mucinous neoplasia: Three case reports. *Virchows Arch* 2009 May;454(5):589–94.
22. Zen Y, Fujii T, Itatsu K, et al. Biliary cystic tumors with bile duct communication: A cystic variant of intraductal papillary neoplasm of the bile duct. *Mod Pathol* 2006 Sep;19(9):1243–54.
23. Choi SC, Lee JK, Jung JH, et al. The clinicopathological features of biliary intraductal papillary neoplasms according to the location of tumors. *J Gastroenterol Hepatol* 2010 Apr;25(4):725–30.
24. Lim JH, Yi CA, Lim HK, Lee WJ, Lee SJ, Kim SH. Radiological spectrum of intraductal papillary tumors of the bile ducts. *Korean J Radiol* 2002;3(1):57–63.
25. Paik KY, Heo JS, Choi SH, Choi DW. Intraductal papillary neoplasm of the bile ducts: The clinical features and surgical outcome of 25 cases. *J Surg Oncol* 2008 May 1;97(6):508–12.
26. Tsuchida K, Yamagata M, Saifuku Y, et al. Successful endoscopic procedures for intraductal papillary neoplasm of the bile duct: A case report. *World J Gastroenterol* 2010 Feb 21;16(7):909–13.
27. Yeh TS, Tseng JH, Chiu CT, et al. Cholangiographic spectrum of intraductal papillary mucinous neoplasm of the bile ducts. *Ann Surg* 2006 Aug;244(2):248–53.

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