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Intraductal papillary neoplasm of the bile duct with rapidly progressive multicentric recurrence: A case report

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ABSTRACT

INTRODUCTION: Knowledge on the pattern of recurrence and prognosis of intraductal papillary neoplasms of the bile duct (IPNB) is limited. Few studies have reported IPNB recurrence in the remnant intrahepatic bile duct, which is indicative of the true multicentricity of IPNB. Herein, we report a case of IPNB with rapidly progressive recurrence in the remnant intrahepatic bile duct and review the literature for discussing the prognosis of IPNB with multicentricity.

CASE PRESENTATION: A 72-year-old male was diagnosed with IPNB in the hepatic duct of segment 3 that had spread to the left hepatic duct. The patient underwent left hepatectomy, total caudate lobectomy, and extra-hepatic bile duct resection with biliary reconstruction. Histologically, the tumor was IPNB with noninvasive adenocarcinoma with a negative surgical margin. Although dilatation of B8 and biliary enzyme elevation were observed beginning at 7–10 months postoperatively, there was no evidence of recurrence. At 17 months postoperatively, the recurrent tumor diffusely spread throughout the remnant intrahepatic bile duct. Internal drainage stents were placed within the intrahepatic bile ducts with relapsed IPNB to relieve jaundice, and a course of chemotherapy was considered. However, the patient did not receive any therapies up to his death at 21 months postoperatively because of rapid disease progression.

CONCLUSION: According to a literature review, some cases of multicentric IPNB have shown rapidly progressive recurrence and poor prognosis. We should consider multicentricity of IPNB even a few months after curative resection, and narrow examinations should also be considered.

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1. Introduction

Intraductal papillary neoplasms of the bile duct (IPNB) are recognized as a subtype of biliary tumors [1] including mucin-producing bile duct tumors, papilloma, and mucinous cystic neoplasms [2]. The pattern of IPNB recurrence has been described in the literature, albeit unclearly. Particularly, reports on multicentric IPNB are rare. Herein, we report a case of IPNB with rapidly progressive recurrence in the remnant intrahepatic bile duct, indicating a possibility of multicentricity. We discuss the clinical course and prognosis and present a literature review. This work has been reported in line with the SCARE criteria [3].

Abbreviations: CHD, common hepatic duct; CT, computed tomography; ERC, endoscopic retrograde cholangiography; IPNB, intraductal papillary neoplasms of the bile duct; LHD, left hepatic duct.

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2. Case presentation

A 72-year-old previously healthy man was referred to our hospital with a complaint of right upper abdominal pain. Laboratory examination revealed elevated hepatic and biliary enzyme levels: total bilirubin, 1.8 (normal range, 0.1–1.2) mg/dl; aspartate aminotransferase, 543 (normal range, 5–30) IU/l; alanine aminotransferase, 233 (normal range, 3–35) IU/l; alkaline phosphatase, 489 (normal range, 90–300) IU/l; and γ -glutamyl transpeptidase, 672 (normal range, 1–28) IU/l. Tumor marker levels (including carcinoembryonic antigen and carbohydrate antigen 19–9) were within normal limits. Contrast-enhanced computed tomography (CT) showed multilocular cystic dilatation and an enhanced mass in the hepatic duct of segment 3 (B3) (Fig. 1a). Drip infusion cholangiography CT showed a defect extending from the left hepatic duct (LHD) to the common hepatic duct (CHD) (Fig. 1b). Endoscopic retrograde cholangiography (ERC) showed an interruption in LHD above the confluence of the main hepatic ducts and a defect with mucin below (Fig. 1c). Intraductal ultrasonography revealed a 15-mm intraductal mass located between LHD and CHD

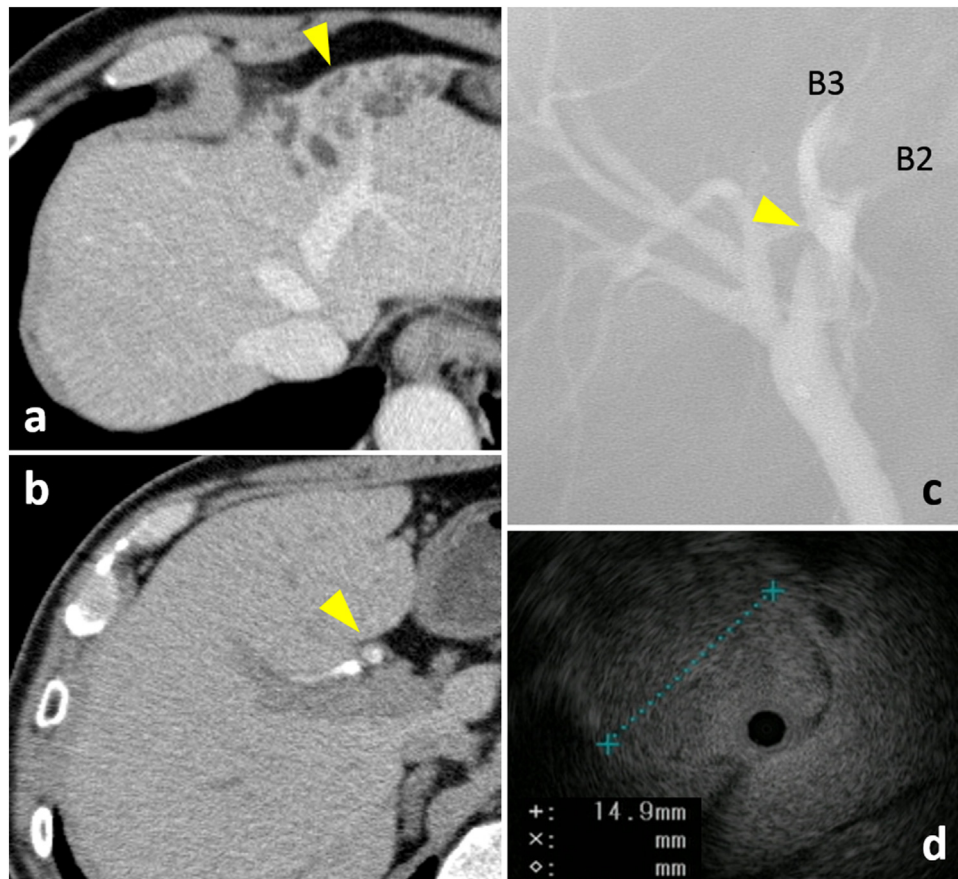


Fig. 1. Preoperative findings.

a CT showed multilocular cystic dilatation and an enhanced mass in B3 (*arrowhead*).

b Drip infusion cholangiography CT showed a defect extending from the left hepatic duct to the common hepatic duct (*arrowhead*).

c ERC showed an interruption in the left hepatic duct above a confluence of main hepatic ducts and a defect with mucin below (*arrowhead*).

d Intraductal ultrasonography revealed a 15-mm intraductal growth type mass located between the left and common hepatic ducts.

(Fig. 1d). Adenocarcinoma was identified following brush cytology. According to these examinations, the patient was diagnosed with B3-dominated IPNB that spread to CHD.

The patient underwent left hepatectomy, caudate lobectomy, extra-hepatic bile duct resection with biliary reconstruction, and regional lymph node dissection. The liver parenchyma of segment 3 was remarkably atrophic. B3 was filled with tumors that appeared as irregular masses on the surface of segment 3 (Fig. 2a). The bile duct stumps were negative for cancer on frozen section examination during the surgery. Specimen cholangiography revealed that all branches of B3 had intraductal tumors. Histologically, the biliary neoplasm comprised atypical epithelial cells arranged in a highly papillary architecture with over secretion of mucin. The neoplasm spread from B3 to LHD (Fig. 2b and c). No invasive growth or lymph node metastases were observed, and the surgical margin was negative. According to these examinations, the tumor was IPNB with noninvasive adenocarcinoma. The postoperative course was uneventful; he was discharged on postoperative day 8. At 7 months postoperatively, dilatation of the hepatic duct of segment 8 (B8) was detected on CT, but it did not appear progressive. At 10 months postoperatively, his biliary enzyme levels were intermittently elevated. There was no evidence of recurrence during frequent CT or magnetic resonance imaging. At 17 months postoperatively, the patient had jaundice, and CT revealed a lesion that had diffusely spread throughout the remnant intrahepatic bile duct (Fig. 3a). Percutaneous transhepatic biliary drainage was performed, and a

drainage stent was placed within the hepatic duct of segment 5 (B5), which was filled with recurrent tumors (Fig. 3b). Bile cytology revealed adenocarcinoma, confirming IPNB relapse. Drainage was insufficient because the remaining intrahepatic bile duct was filled with tumors. Internal drainage stents were placed within B5 and B8 across the anastomosis (Fig. 3c), after which the patient was discharged. Although chemotherapy was considered, owing to liver failure due to rapid progression of the disease, the patient was unable to undergo further treatments and died 21 months postoperatively.

3. Discussion

Studies have discussed unclear patterns of IPNB recurrence. Kim et al. [4] reported recurrence in 12 of 33 patients (36%) with intrahepatic IPNB. Sites of extra-hepatic recurrence were organs (40%), the peritoneum (17%), and the abdominal wall (8%). Further, the incidence of intrahepatic recurrences is unknown. Rocha et al. [5] reported recurrence in 20 of 39 patients (51%) with IPNB, including 35% with locoregional, 35% with distant, and 30% with combined recurrence. Studies have suggested underlying mechanisms of recurrence in the remnant bile duct, such as multicentricity [1,6–8], persistence of atypical epithelium [5,7], and intrabiliary dissemination [8,9]. Although cases of IPNB recurrence in the remnant bile duct have previously been thought to represent multicentric recurrence, Yokode et al. [9] described that true multicentric recurrence

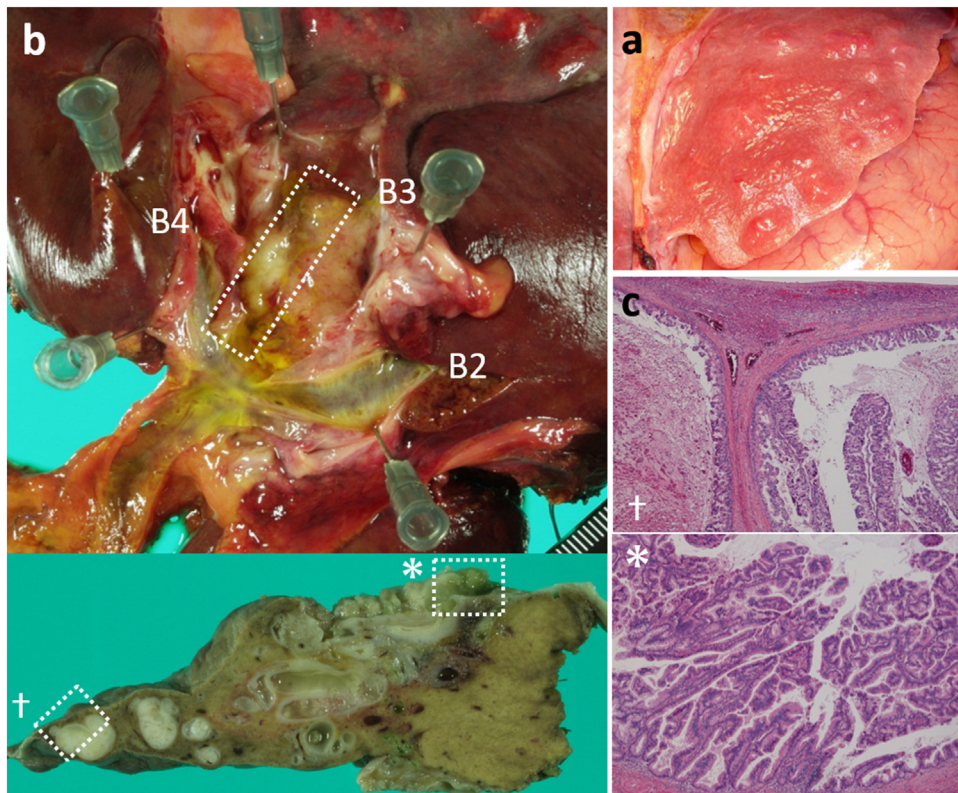


Fig. 2. Operative finding and appearance of resected specimens.

a Liver parenchyma of segment 3 was remarkably atrophic, and B3 filled with tumors were seen as irregular masses on the surface of segment 3.

b,c Macroscopic and microscopic findings of the resected specimen. B3 was filled with a biliary neoplasm comprising atypical epithelial cells arranged in a highly papillary architecture and over secreting mucin.

was less common than that considered initially. Herein, 80% recurrent tumors developed in common bile duct, in contrast to primary IPNB, where 84% tumors develop in intrahepatic or hilar bile ducts [10]. In IPNB, recurrence is more likely to result from dissemination or implantation than from multicentricity.

In the present case, although R0 resection was performed for IPNB with noninvasive adenocarcinoma, recurrence developed in the remnant intrahepatic duct. Therefore, metachronous and multicentric carcinogenesis was mostly considered. However, a possibility of dissemination remained because of no decisive evidence of multicentricity such as similarity between cytology of primary tumor and relapsed tumor.

Biliary enzyme elevation and B8 dilation may have indicated disease relapse; however, recurrence was diagnosed 10 months later because it was difficult to detect recurrence in CT or magnetic resonance imaging.

We conducted a literature review, including the Japanese literature, using PubMed with the key words and phrases “IPNB” and “recurrence” and identified three reports describing IPNB recurrence in the remnant intrahepatic bile duct (Table 1).

Of the four patients, two had slow-growing tumors and were alive after repeated treatment. Laser cauterization and enucleation were effective for localized disease control. The authors described their cases as examples of multicentricity, but they might have represented persistence of atypical epithelium despite the pathologically negative surgical margin because the tumor location was near the stump of the previous operation.

The other two patients had a severe course. The disease recurred in the early phase after R0 resection, and stenting was the only

available treatment. Narita et al. [6] describe a case of recurrence, identified by double-balloon enteroscopy-assisted ERC at 29 months postoperatively. Recurrence possibly occurred during an earlier phase because of the biliary enzyme elevation and cholangitis beginning at 5 months postoperatively. They also determined that CT might be insufficient for detecting recurrence in their case. Consequently, double-balloon enteroscopy-assisted ERC should be considered during the early postoperative phase. Cholangiography or enteroscopy may be necessary for detecting recurrences in the presence of symptoms such as repetitive fever, elevated biliary enzyme levels, or dilation of the remnant intrahepatic bile duct even a few months after curative resection. There is no report about effective treatment for aggressive multicentric recurrence of IPNB. They also describe that liver transplantation might be relevant to consider for IPNB patients with multiple lesions.

4. Conclusions

This was a case of multicentric IPNB with rapid progression and poor prognosis. Literature review reveals that some multicentric IPNB cases exhibit slow-growing characteristics and have a relatively good prognosis, whereas others exhibit characteristics resembling those of our case. We should consider multicentricity in patients with IPNB when they exhibit symptoms, even a few months after curative resection. Furthermore, narrow examinations, such as cholangiography or enteroscopy, should be considered.

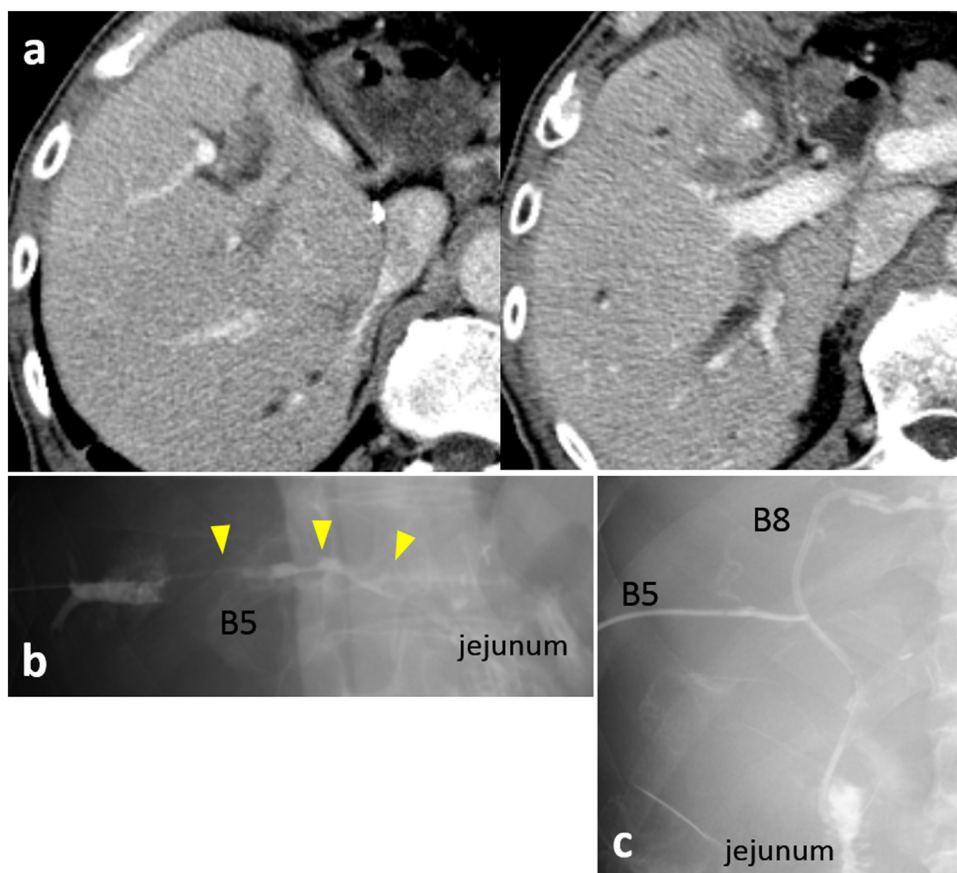


Fig. 3. Images showing recurrent tumor.
a CT showed a lesion diffusely spread in the remnant intrahepatic bile duct.
b A drainage stent was placed within B5 filled with recurrent tumor (*arrowhead*).
c Internal drainage stents were replaced within B5 and B8 across the anastomosis.

Table 1
 Previous reports on intraductal papillary neoplasm of the bile duct with recurrence in the remnant intrahepatic bile duct.

Author (Year)	Age/Sex	No. of tumors	Site	Surgical procedure	SM	Interval to recurrence (months)	Site of recurrence	Treatment for recurrence	Prognosis ^a (months)
Fujita [9] (2005)	74 F	1	n.a.	Left hepatectomy	–	288	lower CBD ~post	Anterior segmentectomy Cholecystectomy	Alive >288
Kurahara [6] (2009)	67 M	1	B4	Medial segmentectomy Left caudate lobe resection Cholecystectomy	–	1 st 6	B1	Laser ablation	Alive 138
						2 nd 7	upper CBD	Enucleation	
						3 rd 28	RHD	Cholecystectomy	
						4 th 2	Post	Laser ablation	
Narita [5] (2015)	78 M	2	RHD CHD	Left hepatectomy Cholecystectomy	–	29	Post	Drainage stent	Dead 41
Our case	72 M	1	B3	Left hepatectomy Cholecystectomy	–	17	Ant Post	Drainage stent	Dead 21

SM: surgical margin, RHD: right hepatic duct, CHD: common hepatic duct, CBD: common bile duct, Post: posterior segmental duct, Ant: anterior segmental duct, n.a.: not available.

^a Term from initial treatment.

Conflicts of interest

No conflict of interest.

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This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethical approval

The ethical approval has been exempted by our institution because this is a case report.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A

copy of the written consent is available for review by the Editor-in-Chief of this journal upon request.

Author contribution

YK prepared the draft of the report and collected data. RY supervised the treatment of the patient and edited the manuscript. SW and KA assisted in preparing the manuscript. FS and AA contributed to drafting the manuscript. All authors have read and approved the final manuscript.

Registration of research studies

Not applicable.

Guarantor

Yumiko Kageyama and Ryuzo Yamaguchi.

References

- [1] Y. Zen, T. Fujii, K. Itatsu, K. Nakamura, H. Minato, S. Kasashima, et al., Biliary papillary tumors share pathological features with intraductal papillary mucinous neoplasm of the pancreas, *Hepatology* 44 (2006) 1333–1343.
- [2] Y. Nakanuma, Y. Sato, K. Harada, M. Sasaki, J. Xu, H. Ikeda, Pathological classification of intrahepatic cholangiocarcinoma based on a new concept, *World J. Hepatol.* 2 (2010) 419–427.
- [3] R.A. Agha, A.J. Fowler, A. Saetta, I. Barai, S. Rajmohan, D.P. Orgill, for the SCARE Group, The SCARE statement: consensus-based surgical case report guidelines, *Int. J. Surg.* 34 (2016) 180–186.
- [4] W.J. Kim, S. Hwang, Y.J. Lee, K.H. Kim, K.M. Park, C.S. Ahn, et al., Clinicopathological features and long-term outcomes of intraductal papillary neoplasms of the intrahepatic bile duct, *J. Gastrointest. Surg.* 20 (2016) 1368–1375.
- [5] F.G. Rocha, H. Lee, N. Katabi, R.P. DeMatteo, Y. Fong, M.I. D'Angelica, et al., Intraductal papillary neoplasm of the biliary duct: a biliary equivalent to intraductal papillary mucinous neoplasm of the pancreas? *Hepatology* 56 (2012) 1352–1360.
- [6] M. Narita, B. Endo, Y. Mizumoto, R. Matsusue, H. Hata, T. Yamaguchi, et al., Multicentric recurrence of intraductal papillary neoplasms of bile duct in the remnant intrahepatic bile duct after curative resection, *Int. J. Surg. Case Rep.* 12 (2015) 123–127.
- [7] H. Kurahara, H. Shinchi, Y. Mataka, S. Maeda, S. Natsugoe, S. Takao, A long-term survival case of mucin-producing bile duct carcinoma treated with repetitive surgical procedure, *Jpn. J. Gastroenterol. Surg.* 42 (2009) 510–515 (In Japanese).
- [8] T. Fujita, T. Ajiki, H. Sawa, Y. Mita, H. Hori, Y. Fujino, et al., A case of mucin-producing intrahepatic cholangiocarcinoma recurred 24 years after resection, *JJBA* 19 (2005) 500–504 (In Japanese).
- [9] M. Yokode, Y. Yamashita, Y. Zen, Biliary intraductal papillary neoplasm with metachronous multiple tumors – true multicentric tumors or intrabiliary dissemination: a case report and review of the literature, *Mol. Clin. Oncol.* 6 (2017) 315–320.
- [10] K. Fujikura, T. Fukumoto, T. Ajiki, K. Otani, M. Kanazawa, M. Akita, et al., Comparative clinicopathological study of biliary intraductal papillary neoplasms and papillary cholangiocarcinomas, *Histopathology* 69 (2016) 950–961.

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