Int Surg 2019;**104:**358–363
DOI: 10.9738/INTSURG-D-16-00105.1

Case Report

Resection for a Recurrent Mucus-Producing Cholangiocarcinoma After Surgery: a Case Report

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Introduction: Intraductal papillary neoplasm of the bile duct (IPNB) is a variant of bile duct carcinoma characterized by intraductal growth. There are few case reports and papers discussing treatment policy and prognosis for cases of postoperative relapse.

Case Presentation: The case subject was a female in her 40s. Due to IPNB with the primary tumor in hepatic left lobe, the patient underwent hepatic left lobe, caudate lobe, and bile duct resection, and biliary tract reconstruction at another institution. Four years later, near the cholangiojejunostomy, a localized recurrence was indicated. Though systemic metastasis was examined with CT, FDG-PET, distant metastasis was not confirmed. As it was believed that resection of the recurrent focal could lead to a long-term survival, the recurrent focal was resected. The resected specimen was a cystic mass with a film, and in a pathologic examination, lymph node tissue was not confirmed in the specimen, while intracystic papilloma of attached liver tissue without continuity was confirmed. The patient has not seen a relapse for 5 years and 5 months after the second surgery.

Conclusion: In a case of localized recurrence after the IPNB surgery, resection should be actively considered.

Key words: IPNB – Localized recurrence – Postoperative relapse

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Intraductal papillary neoplasm of bile duct (IPNB) is an epithelial tumor occurring from the bile duct and was a concept that was proposed relatively in recent years.[1] It is a generic name for relatively rare diseases characterized by intrahepatic cystic lesion and mucus production. Its growth is gradual, and distant metastasis is not common.[2] If metastasis to lymph node is not confirmed, and if the depth of tumor invasion is limited to the fibromuscular layer, prognosis is considered to be good compared to normal bile duct cancer.[3] On the other hand, there are not many case reports, and there are no papers discussing treatment policy and prognosis for cases of postoperative relapse.

We report our experience with an interesting case of IPNB where a long-term survival was made possible through resection of localized recurrence that occurred 4 years after the initial surgery, with bibliographical consideration.

The Case and Results

The patient was a 41-year old female whose primary complaint was abdominal pain. The abdominal pain began in July 2004, and the patient was diagnosed with IPNB at another institution as a mucus-producing papillary tumor was confirmed in the hepatic left lobe. During the same month, enlarged hepatic left lobe bile duct was resected and a cholangiojejunostomy was performed. The pathologic diagnosis was mucin-producing bile duct cancer, resection stump was negative, and there was no metastasis to the lymph node. Results of immunohistochemical examination for tumor tissue were negative for MUC1 and MUC2, and positive for MUC5AC. Postoperative course was good, and the patient was being observed as an outpatient. But abdominal CT performed in July 2008 indicated a cystic lesion with a diameter of 2 cm in the area in contact with the liver resection posterior to the cholangiojejunostomy. Recurrence of IPNB was suspected and the patient was introduced to Division of Hepato-Biliary-Pancreatic Surgery, Kobe University, on August 2008. Medical history: type B chronic hepatitis at 30, and paracentesis of a liver cyst was performed at 31. Family history: nothing to note. Conditions at the time of admission: height of 157 cm and body weight of 47 kg. The abdomen was flat and soft without any tenderness, and liver, spleen, and tumor mass were not palpable. Yellowing of bulbar conjunctiva was not confirmed. Blood test findings at the time of admission: CA19-9 of 7 U/mL and CEA of 0.8 ng/mL. Abnormal values were not observed in these tumor markers or others, and in biliary enzymes, etc.

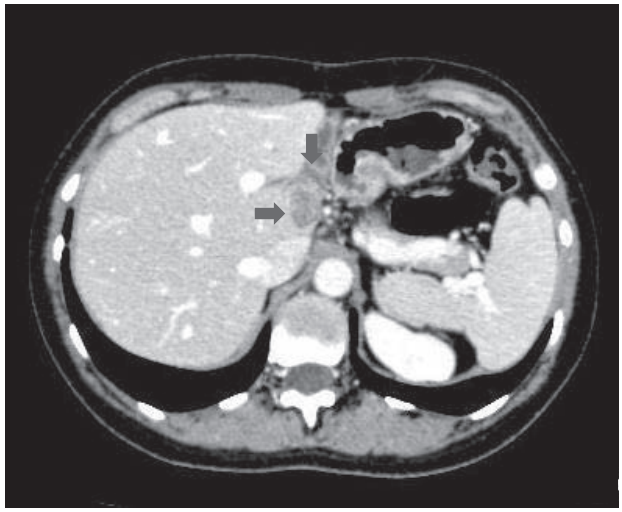

Fig. 1 Abdominal CT scan: Low intensity tumor mass of 25 × 30 mm without contrast effect but with clear boundary is confirmed on the dorsal side of the cholangiojejunostomy and caudate lobe stump (arrow).

Abdominal CT scan: Low intensity tumor mass of 25 × 30 mm was confirmed in dorsal side of the cholangiojejunostomy and stump of caudate lobe. Contrast effect was not confirmed, and boundary with the surrounding was clear (Fig. 1). DIC-CT scan: Caudate lobe branch could not be visualized well on the hepatic portal side. Posterior segmental branch was far from the tumor mass, and though anterior segmental branch was close to the tumor mass, a clear disruption was not confirmed (Fig. 2). Abdominal MRI scan: A tumor mass of 25 mm diameter was

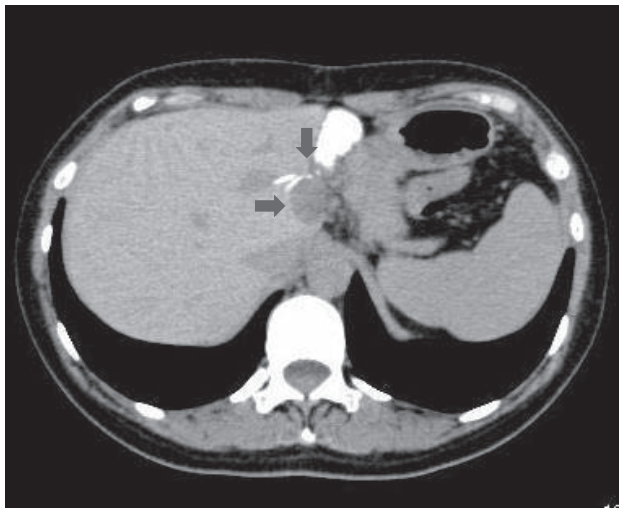

Fig. 2 DIC-CT scan: Anterior segment branch is close to the tumor mass, but clear disruption is not confirmed (arrow).

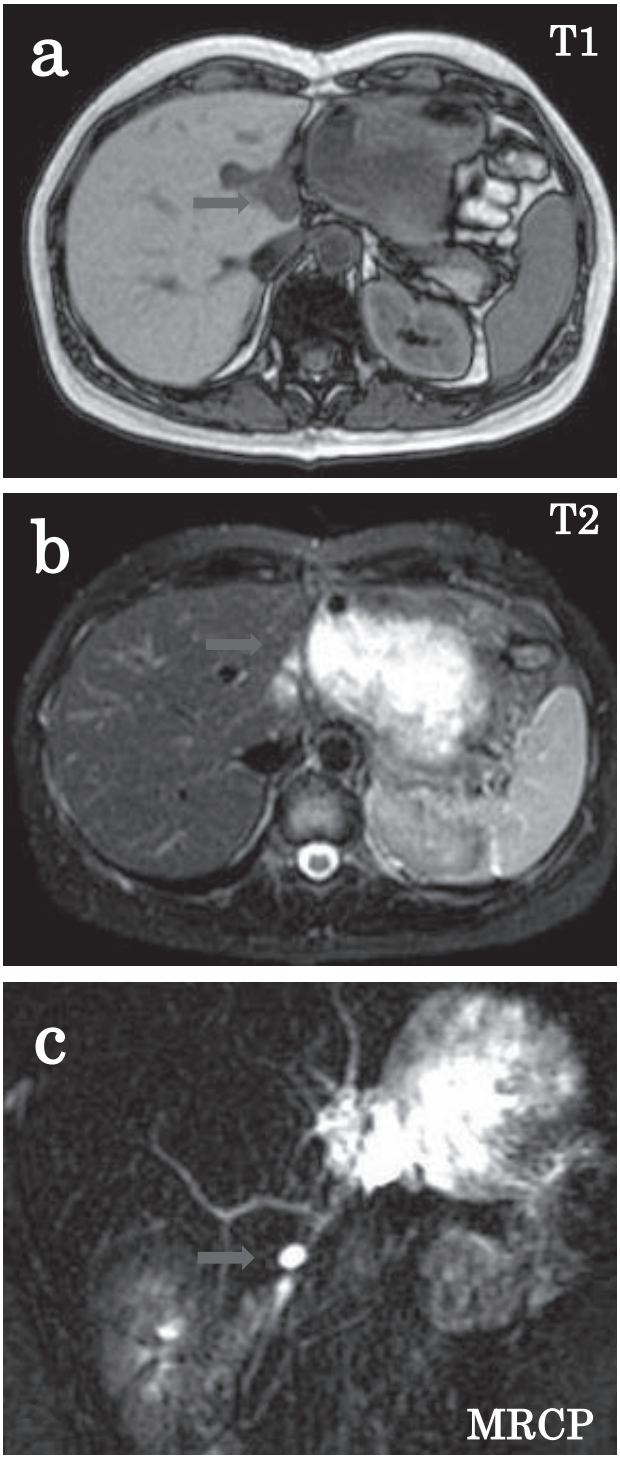

Fig. 3 a. Abdominal MRI scan: the tumor mass of 25 mm in diameter is shown as low signal in T1-weighted image in the liver resection stump (arrow). b Abdominal MRI scan: the tumor mass of 25 mm in diameter is shown as high signal in T2-weighted image in the liver resection stump (arrow). c. MRCP scan: cystic legion was confirmed on the caudal side of the junction between liver S4 segment branch and anterior segment branch, and dorsal side of the cholangiojejunostomy (arrow). Enlargement of periphery bile duct was not confirmed.

confirmed through weak signal in T1-weighted image (Fig. 3a) and strong signal in T2-weighted image of the liver resection stump (Fig. 3b). In MRCP, cystic lesions were confirmed on the caudal side of the junction between S4 segment branch and anterior segment branch, and dorsal side of the cholangiojejunostomy. Compared to the diameter of the tumor mass, periphery bile duct was not enlarged; therefore, a lesion was suspected outside of bile duct (Fig. 3c).

FDG-PET scan: Though circumscribed collection (SUVmax: 5.8) of FDG was confirmed near the liver caudate lobe, distant metastasis was not confirmed.

Surgery: In laparotomy findings, the tumor mass was projecting out of the liver in contact with the liver resection stump on the dorsal side of the hepatic duct jejunal anastomosis. The hepatic duct jejunal anastomosis is resected for a moment, and as not to leave cancer in the resection stump, the tumor was resected from the surrounding tissues while leaving some liver tissues attached, but part of it was strongly adhered to left portal vein and inferior vena cava, making removal difficult. After removing the tumor mass as much as possible, hepatic duct jejunal re-anastomosis was performed (Figs. 4a and 4b). Pathologic findings: The tumor mass has fibrous film, consisting of solid component and mucus component. Tumor cells with papillary and tubular structure have spread while producing mucus, and the histopathologic diagnosis was mucinous adenocarcinoma. This is consistent with histopathologic findings from the initial surgery, and thus it was considered to be a recurrent lesion. Lymph node tissue was not found in the tumor mass. The image of healthy bile duct was confirmed in parts of tissues surrounding neoplastic cystic lesions, but there was no connectivity with the bile duct of attached liver tissues (Figs. 5a and 5b). Postoperative course: Seven days after the surgery, discharge of bile from the drain installed on the dorsal side of the hepatic duct jejunal anastomosis was confirmed, and it was diagnosed as a suture failure in the hepatic duct jejunal part. It improved through a conservative treatment, and the patient was discharged 46 days after the surgery. Currently, the patient has not experienced a relapse 4 years and 9 months after the surgery (8 years and 9 months since the first surgery). In addition, postsurgical stenosis was not confirmed in the reconstructed hepatic duct jejunal

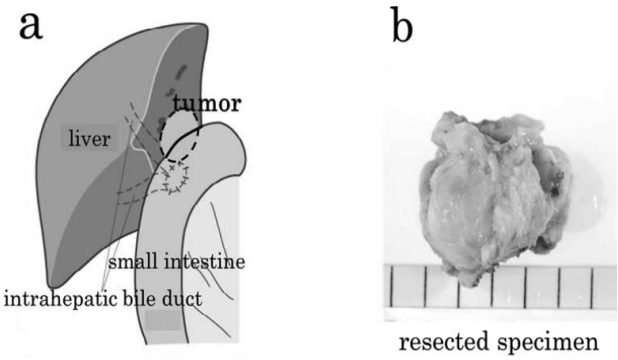

Fig. 4 a. Laparotomy findings: the tumor mass is on the dorsal side of the hepatic duct jejunal anastomosis and protrudes from the liver in contact with the liver resection stump. b. Mucus can be confirmed in the cyst on the resection surface of the specimen.

anastomosis, and there is no record of hospitalization due to cholangitis.

Discussion

In the present case, localized recurrence was confirmed in the hepatic duct jejunal anastomosis four years after resection of enlarged left lobe, resection of bile duct, and cholangiojejunostomy were performed for a mucus-producing cystic primary tumor in the hepatic left lobe. Based on the histopathological examination of resected specimen from the first surgery and the cystic tumor of the present resection, and the site of tumor localization, it was considered to be relapse of IPNB.

IPNB is a generic name for relatively rare diseases characterized by intrahepatic cystic lesion in epithelial tumor occurring in intrahepatic bile duct epithelium, papillary growth of tumor, and mucus production. It is similar to intraductal papillary mucinous neoplasm of the pancreas (IPMN).[1] IPNB is an overall concept that includes precancerous lesion to advanced cancer and based on differences in their biologic properties, pathologic conditions such as clinical symptoms, histologic picture, and prognosis are diverse. In advanced tumors, histopathologic characteristic is papillary tumor in the bile duct and mucus production, but as precancerous lesion of bile and biliary ducts or early-stage cancerous legions, WHO classified it based on its histologic type as flat biliary intraepithelial neoplasia (BilIN) and papillary intraductal papillary neoplasm of bile duct (IPN).[4] It has also been indicated that its differences in its occurrence or malignant transformation process may impact biologic properties. As for similarity with IPMN, same as in IPMN, there is a report of tumor cells that express MUC2, MUC5AC, and CK20, which are intestinal metaplasia myxoid of gastric foveolar.[5] MUC5AC was expressed in the present case as well. The present case subject was in her 40s, but this disease is generally more common in older individuals, and its clinical symptoms include fever, abdominal pains, and jaundice, which are symptoms based on bile duct blockage and cholangitis due to tumor-produced mucus. Only about 7% of patients are asymptomatic, and its growth rate is slower than normal bile duct cancer; therefore, the duration is said to be long. Predilection site is often the left lobe (and caudate lobe) compared to the right lobe,[6] and style of progress for the tumor is surface expansion in 45% to 57%.[2,3,7,8] The depth of invasion is shallow at the mucosal layer and fibromuscular (fm) layer for about 53% of all cases. If the depth of invasion is the mucosal layer or fm layer, metastasis to lymph node and vascular invasion are hardly ever confirmed[3]; therefore, in the early stage, compared to normal bile duct cancers, prognosis is good, and if curative resection could be performed, 5-year survival rate is relatively good at 31∼80%.[5,7–10] On the other hand, if the depth of invasion is subserosa (ss layer) or deeper, similar to normal bile duct cancers, distant metastasis to peritoneum, liver, lung, and spleen is confirmed, and vascular invasion and metastasis to lymph node is confirmed for about 27% of cases.[2,3] As postoperative recurrence cases are not rare, for

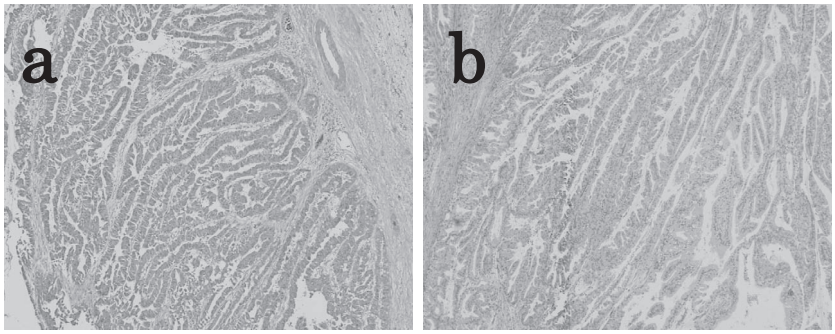

Fig. 5 Histopathologically findings: a. The initial resection specimen. Tumor cells with papillary and tubular structure grew with mucus production (×400). b. The resection specimen from the present case. It has fibrous film, and mucus-producing tumor cells with papillary and tubular structure are growing (×400).

IPNB, in the same manner as for normal bile duct cancers, systemic chemotherapy using gemcitabine hydrochloride[11] and 5FU[12] and radiation therapy[13] for resection stump are being attempted as the adjunctive therapy. In addition, many recurrence case in hepatic bile duct stump after IPNB resection had negative bile duct stump at the time of resection; therefore, the average time for the relapse from the first surgery is said to be four years.[14] Many IPNB cases were treated with surgery, but long-term survival following the second surgery is not common as in the present case. The present case was diagnosed as IPNB in the histopathologic diagnose in the first surgery. There was no metastasis to the lymph node, and the depth of invasion was mostly the m layer though there were some up to the fm layer; and thus, the risk of relapse was low. The level of malignancy was low as relapse occurred four years after the first surgery, gradual growth of tumor was estimated, the site of relapse is solitary—limited to the dorsal side of the cholangiojejunostomy—and distant metastasis was not confirmed in full body CT and FDG-PET; therefore, it was assumed that resection of the recurrent focal would lead to a long-term survival, and surgical reresection was chosen. Histopathologically, it was diagnosed as the relapse of IPNB, and there has been no relapse at the present day at 5 years and 5 months later. The style of relapse in the present case is that the site in which relapse of tumor was confirmed was the hepatic duct resection stump, in other words, the dorsal side of the hepatic duct jejunal anastomosis. In the specimen resected during the first surgery, the bile duct stump was negative, and atypia was not confirmed. The time of relapse was relatively long (4 years after the initial surgery), the pathologic examination of relapsed tumor that was resected in the present case did not confirm connectivity to lymph node tissue, normal bile duct in attached liver tissue, or atypical epithelium of bile duct in liver tissue, while cystic lesion with atypical bile duct in some tissues are confirmed; therefore, it is not a relapse due to peritoneal dissemination, but tumor cells in bile duct mucus was implanted during the operation of the initial surgery and relapsed near the resection stump 4 years later, or skip lesion was present in the remaining bile duct in the previous surgery, leading to a relapse. The style of IPNB growth as described earlier was surface expansion in addition to the invasion of the bile duct wall. In surgery, bile duct resection that takes negative stump into consideration is important, and lymph node dissection according to the normal bile duct cancer for this purpose is also important. Even if the bile duct resection stump is negative, attention should be paid to the level of atypia, and from the perspective of intraoperative implantation prevention from cancer cells in bile mucus, a care must be taken not to spill bile mucus. Literature examination in Japan showed that the recurrence of mucus-producing cholangiocarcinoma after a radical surgery exhibited cancerous peritonitis,[12] recurrence of PTCD fistula,[15] and report of recurrence in remaining bile duct,[16] and there are reports of what could be implantation or bile duct stump relapse. We examined a case of re-resection for IPNB case with high likelihood of relapse from remaining bile duct from resection 24 years ago,[17] but there still is no case of long-term survival after a surgery on solitary recurrence as in the present case. Since IPNB can relapse long after the initial surgery due to its property, bile in the bile duct resection stump must be handled carefully during a surgery, and after the initial surgery, it is important to continue observing the course for systemic metastasis for a long time. If relapse is confirmed, after systemic examination for distant metastasis, etc., active surgical resection should be considered.

References

1. Nakamura Y. Biliary tract clinicopathology with an emphasis on biliary intraepitherial neoplasm (BilIN). *JJBA* 2011;**25(**1):31–42
2. Zen Y, Fuji T, Itatsu K, Nakamura K, Minato H, Kasashima S. Biliary papillary tumors share pathological features with intraductal papillary mucinous Neoplasm of the pancreas. *Hepatology* 2006;**44**(5):1333–1343
3. Ostuka M, Kimura F, Miyazaki M, Yoshitome H, Kato A, Nozawa S *et al*. Modes of spread of mucin-producing bile duct tumor. *J Biliary Tract Pancreas* 2006;**27**(7):465–469
4. Albores-Saavedra J, Kloppel G, Adsay NV, Menck HR, Scoazec JC, Soehendra N *et al*. Carcinoma of the gallbladder and extrahepatic bile ducts. In: Bosman FT, Carnerio F, Hruban RH, Theise ND, eds. *WHO Classification of Tumors of the Digestive System*. 4th ed. Lyon: IARC; 2010:266–273.
5. Nakamura Y, Keita Itatsu K, Yoh Zen Y. Intraductal papillary neoplasm of bile duct (IPNB)-Proposal and pathologic spectrum of a new disease entity. *JJBA* 2007;**21**(1):45–54
6. Yokoi K, Akio Harada A, Hiroya Murakami H, Yoshida S, Yaguchi T, Komatsu Y. Mucin-producing bile duct cancer of the hepatic hilar region which was resected after elapsing for a four-years course. *J Jpn Surg Assoc* 2000;**61**(2):462–466
7. Chen MF, Jan YY, Chen TC. Clinical studies of mucin – producing cholangiocellularcarcinoma: a study of 22 histopathology-proven cases. *Ann Surg* 1998;**227**(1):63–69

8. Sakamoto E, Nimura Y. Mucin-producing cholangiocarcinoma. *Clin Gastroenterol* 1998;**13**(11):1611–1617
9. Yamaguchi K, Tanaka M. Is IPN-B a Counter part of IPMN? *J Biliary Tract Pancreas* 2008;**29**(6):517–522
10. Igami T, Nagino M, Yuasa N, Oda T, Nishio H, Nimura Y *et al*. Mucin-producing bile duct tumors: in comparison with mucin-producing pancreatic tumors. *Kan tan sui* 2006;**52**(2): 510–515
11. Shinshi A, Takekawa K, Mochizuki T, Ohta H, Ida K, Okiyama H *et al*. A case of mucin-producing cholangiocarcinoma with characteristic lymph node metastasis. *J Biliary Tract Pancreas* 2006;**29**(10):967–970
12. Yamade N, Tabuse Y, Kobayashi Y. A case of mucin-producing intrahepatic cholangiocarcinoma with peritoneal disseminations due to extrahepatic growth and rupture of tumor. *J Wakayama Med Soc* 2006;**57**(4):141–146
13. Kishiwada M, Tabata M, Isaji H, Kato H, Azumi Y, Osawa I *et al*. A case of mucin-producing intrahepatic cholangiocarcinoma with superficial growth. *Therapeutic Res Hepato-Biliary-Pancreatic Dis* 2008;**68**(1):60–65
14. Ito E, Watanabe J, Takada Y, Hatano M, Kushihata F, Takada Y. A case of intraductal papillary neoplasm of bile duct, which recurred 4 years after primary curative resection. *J Jpn Surg Assoc* 2013;**74**(3):91–796
15. Sakamoto E, Hayakawa N, Kamiya J, Kondo S, Nagino M *et al*. Treatment strategy for mucin-producing intrahepatic cholangiocarcinoma; value of percutaneous transhepatic biliary drainage and cholangioscopy. *World J Surg* 1993;**23**(10):1038–1043
16. Kurahara H, Shinchi H, Mataki Y, Maeda S, Natsugoe S, Takao S. A long-term survival case of mucin-producing bile duct carcinoma treated with repetitive surgical procedure. *Jpn J Gastroenterol Surg* 2009;**42**(5):510–515
17. Fujita T, Ajiki T, Sawa H, Hori H, Mita Y, Kuroda Y *et al*. A case of mucin-producing intrahepatic cholangiocarcinoma recurred 24 years after resection. *JJBA* 2005;**19**(4):510–515