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Multicentric recurrence of intraductal papillary neoplasms of bile duct in the remnant intrahepatic bile duct after curative resection



Masato Narita^{a,*}, Bunji Endo^b, Yoshinori Mizumoto^b, Ryo Matsusue^a, Hiroaki Hata^a, Takashi Yamaguchi^a, Tetsushi Otani^a, Iwao Ikai^a

^a Department of Surgery, National Hospital Organization, Kyoto Medical Center, 1-1 Mukaihata-cho, Fukakusa, Fushimi-ku, Kyoto 612-8555, Japan

^b Gastroenterology, National Hospital Organization, Kyoto Medical Center, 1-1 Mukaihata-cho, Fukakusa, Fushimi-ku, Kyoto 612-8555, Japan

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ABSTRACT

INTRODUCTION: There have been few reports on the prognosis of patients with intraductal papillary neoplasms of the bile duct (IPNB). Here we report a case of IPNB in a patient with early-stage carcinoma who had multicentric recurrence in the remnant hepatic bile duct after curative resection.

CASE PRESENTATION: A 78-year-old man with hepatic dysfunction and cholestasis was referred to our hospital. Preoperative imaging studies revealed the presence of papillary tumors in the left hepatic duct and common hepatic duct, while no tumor lesions were detected in the right hepatic duct. This patient underwent left hepatectomy, extra-hepatic bile duct resection with biliary reconstruction, and regional lymphnode dissection. On the basis of pathological examination, this patient was diagnosed with multiple IPNB with early-stage adenocarcinoma with negative surgical margin. Postoperative work-up was periodically performed, indicating no evidence of recurrence, while the patient had sustained hepatic dysfunction, cholestasis, and repetitive cholangitis since the early postoperative period. Finally, recurrence in the remnant intrahepatic bile duct of the posterior segment was revealed by double balloon enteroscopy at 29 months after surgery. At 34 months after surgery, internal drainage stents were replaced in both endoscopic and percutaneous manners within the relapsed intrahepatic bile ducts to address repetitive cholangitis. These procedures enabled the patient to remain asymptomatic until death at 41 months after surgery.

DISCUSSION: Multicentric recurrence in the remnant intrahepatic bile duct after surgery may occur in IPNB patients with multiple lesions. An endoscopic approach may be useful in such cases, not only in the diagnosis of remnant intrahepatic bile duct recurrence but also for palliation of symptoms.

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1. Introduction

Intraductal papillary neoplasm of the bile duct (IPNB) is a newly-recognized disease and is categorized as a subtype of biliary cystic tumor in the World Health Organization classification of 2010 [1]. IPNB is defined as a biliary epithelial tumor with exophytic nature, exhibiting a papillary mass within the bile duct lumen and with a prominent intraductal growth pattern. It has been identified as the biliary counterpart of intraductal papillary mucinous neoplasm of the pancreas (IPMN) [2]. Despite a growing number of publications on IPNB, its long-term prognosis and pattern of recurrence remain poorly understood.

Here we report a case of relapsed IPNB with suspected metachronous multicentric recurrence in the remnant hepatic bile duct at 29 months after curative resection. The clinical course of

the patient was reviewed, and the prognosis of IPNB was discussed in the context of relevant literature.

2. Case presentation

A 78-year-old man was referred to our hospital for evaluation of right upper quadrant pain persisting for 2 days. Laboratory examination revealed cholestasis [total bilirubin, 3.9 mg/dL; alkaline phosphatase (ALP), 986 IU/L; gamma-glutamyltranspeptidase (γ -GTP), 587 IU/L] and hepatic dysfunction [aspartate aminotransferase (AST), 603 U/L; alanine aminotransferase (ALT), 414 U/L]. Contrast-enhanced computed tomography (CE-CT) showed dilatation of the intrahepatic bile duct in the left hemiliver and the extrahepatic bile ducts and a mass lesion in the left hepatic duct (Fig. 1A). Endoscopic retrograde cholangiography (ERC) revealed the presence of multiple blood clots at the ampulla of Vater and filling defects within the left hepatic duct (Fig. 1B). Peroral cholangioscopy (POCS) revealed papillary tumors without mucin production at the orifice of the left hepatic duct, while no tumor

* Corresponding author. Tel.: +81 756419161.

E-mail address: narinari@kuhp.kyoto-u.ac.jp (M. Narita).

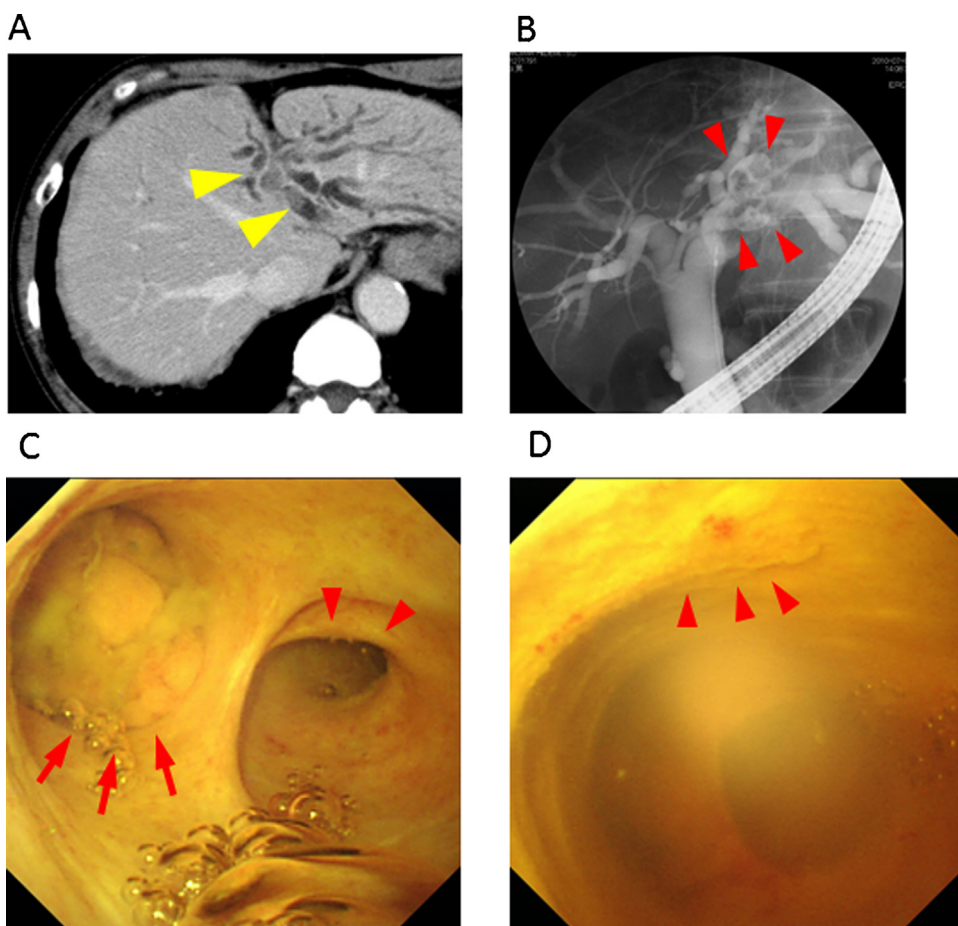


Fig. 1. Preoperative imaging studies: (A) Contrast-enhanced computed tomography (CE-CT): Arrowheads show solid lesions in the left hepatic duct. (B) Endoscopic retrograde cholangiography (ERC): Arrowheads indicate filling defects in the left hepatic duct. (C–D) Peroral cholangioscopy: (C) Arrowheads indicate the orifice of the right hepatic duct. No tumor lesions are presented. Arrows indicate the orifice of the left hepatic duct which is completely filled with papillary tumors. (D) Arrowheads indicate papillary tumors located in the common hepatic duct.

lesions were observed right hepatic duct (RHD; Fig. 1C). A papillary tumor was also detected in the common hepatic duct (CHD), which was located separately from the tumors in the left hepatic duct (Fig. 1D). Both papillary tumors were biopsied, and pathological examination of biopsy specimens revealed well-differentiated adenocarcinoma of the bile duct. Moreover, negative biopsies were performed from the biliary epithelium at the hilar and RHD; on pathological examination, normal biliary epithelium was confirmed in these biopsy specimens. Based on these examinations, the patient was diagnosed with left side-dominated intraductal growth-type cholangiocarcinoma. There was no evidence of distant metastases. We planned a surgical intervention with curative intent.

The patient underwent left hepatectomy with left-sided caudate lobectomy, extra-hepatic bile duct resection with biliary reconstruction, and regional lymphnode dissection. Stumps of bile duct (RHD and CHD) were negative for cancer by frozen section examination during surgery. The duration of the operation was 544 min, with blood loss amounting to 600 g without blood transfusion. By gross appearance, two papillary tumors were observed in the left main hepatic duct and CHD in a discontinuous manner (Fig. 2A). Microscopically, these tumors were diagnosed as pancreatobiliary-type adenocarcinoma (Fig. 2B). Tumor invasion was limited to the mucosal layer, and lymphatic-vascular involvement was not evident. There was no lymphnode metastasis (0/19), and the surgical margin was negative. The patient was diagnosed with multiple IPNB with early-stage adenocarcinoma. The postoperative course

was uneventful, and the patient was discharged 27 days after surgery.

After surgery, 8-weekly assessments of blood tests and 6-monthly abdominal CE-CT scans were performed. No recurrence was documented until 24 months after surgery; however, biliary enzymes, including ALP and γ -GTP, had been substantially elevated since 5 months after surgery. The patient sustained mild cholangitis twice during this period, which was cured within 2 days by intravenous antibiotics. At 29 months after surgery, the patient was admitted to our hospital with fever due to cholangitis. Upon CT imaging, an anastomotic stenosis of the hepaticojejunostomy was suspected (Fig. 3A). Double-balloon enteroscopy (DBE) was performed, revealing papillary tumors protruding from the anastomotic orifice of the hepaticojejunostomy (Fig. 3B). DBE-assisted ERC showed filling defects throughout the posterior branch of the hepatic duct (Fig. 3C and D). Pathological examination of biopsy specimens revealed well-differentiated pancreatobiliary-type adenocarcinoma. This result confirmed that cholangitis occurred because of relapsed IPNB in the intrahepatic bile ducts of the posterior segment. After discharge, the patient suffered repetitive cholangitis, forcing him to be admitted to the hospital each time. At 34 months after surgery, plastic stents were endoscopically placed within the hepatic duct of segment 6 (B6) and segment 7 (B7) in an attempt to improve chronic cholestasis. CE-CT was performed following this procedure and revealed insufficient drainage of B6. An additional internal drainage tube was percutaneously placed into B6 across the anastomosis. These procedures improved the general

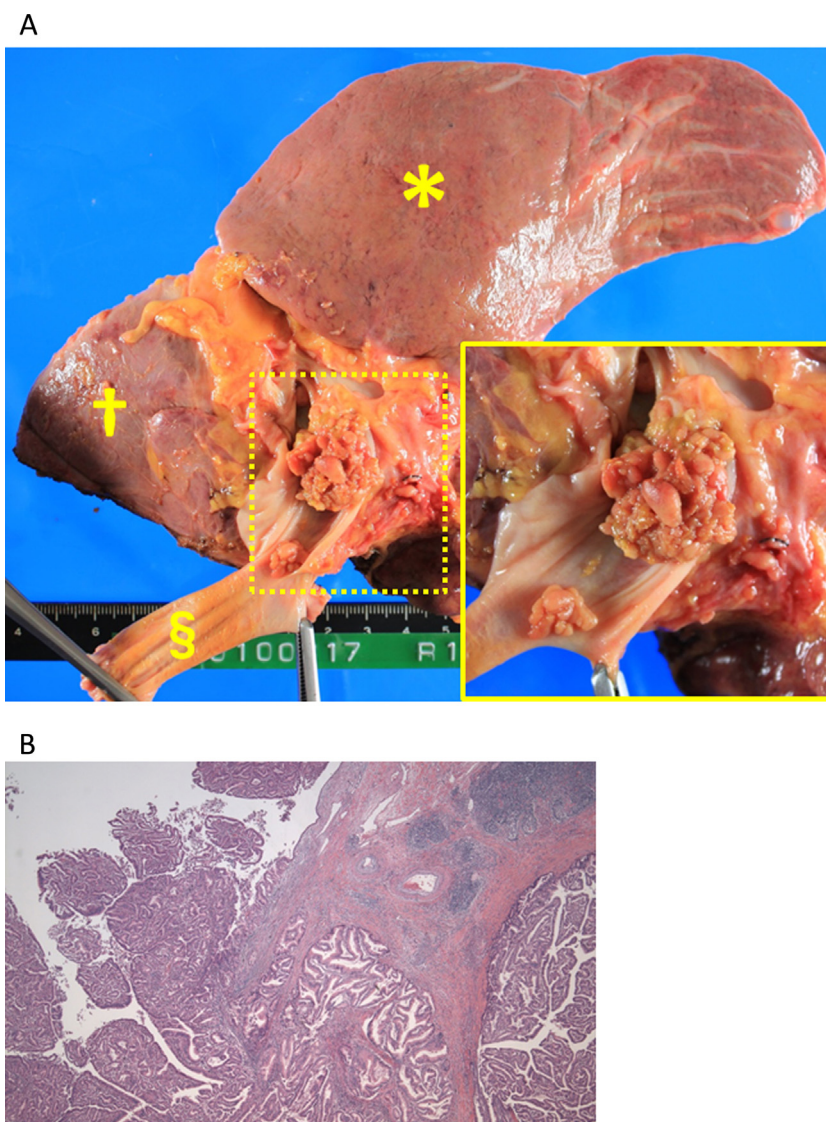


Fig. 2. (A) Gross appearance of resected specimens: *, †, and § correspond to liver parenchyma of segment 2+3, liver parenchyma of segment 4, and common bile duct, respectively. The photograph enclosed by the solid line indicates magnification of the area enclosed by the dotted line. (B) Tumor microscopy image indicating the presence of pancreaticobiliary-type adenocarcinoma.

condition of the patient, who remained asymptomatic until death at 41 months after surgery.

3. Discussion

Owing to the novelty of its disease concept, there have been few reports on the prognosis of patients with IPNB. Jung et al. reported on the prognosis of 93 patients with IPNB undergoing surgery according to the arbitrary-defined classification [3]. In the study, twenty-six patients had mucosa-confined cholangiocarcinoma, and the 5-year-survival and disease-free-rate of these patients was approximately 90% and 85%, respectively, while the prognosis of patients undergoing R0 resection was unclear because 9/26 patients underwent surgery with R1 resection. Kim et al. reported on the long-term outcome of 97 patients with IPNB who underwent surgery [4]. Of 90 patients undergoing R0 resection, 22 (24.4%) developed tumor recurrence following surgery. Among them, 17 (77.8%) developed local tumor recurrence despite R0 resection, while there was no description of the details of preoperative assessment and diagnosis of recurrence. In this context, which

patients had local or remnant intrahepatic bile duct recurrence remains unclear.

In the present case, preoperative assessment of the entire biliary tract was rigorously performed using ERC and POCS, and absence of tumor lesions within the hepatic duct of the future remnant liver was confirmed. Furthermore, a negative resection margin was confirmed by frozen section during surgery, and the present case underwent R0 resection. Pathological examination revealed mucosa-confined cholangiocarcinoma and multiple lesions at the common hepatic duct. Therefore, this suggests that IPNB with multiple lesions may have a possibility of leading to multicentric recurrence in the remnant intrahepatic bile duct. If so, surgical resection may not be sufficient in IPNB patients with multiple lesions, although R0 resection is achieved. How these patients should be treated remains to be answered. Liver transplantation for patients with intrahepatic cholangiocarcinoma (ICC) is considered to be contraindicated in most transplant centers because data from larger cohort studies confirmed poor post-transplant outcomes in patients with ICC [5–7]. However, recent data show excellent outcomes in selected patients, such as patients with solitary ICCs ≤ 2.0 cm and no lymph node metastasis [8,9]. IPNB is a

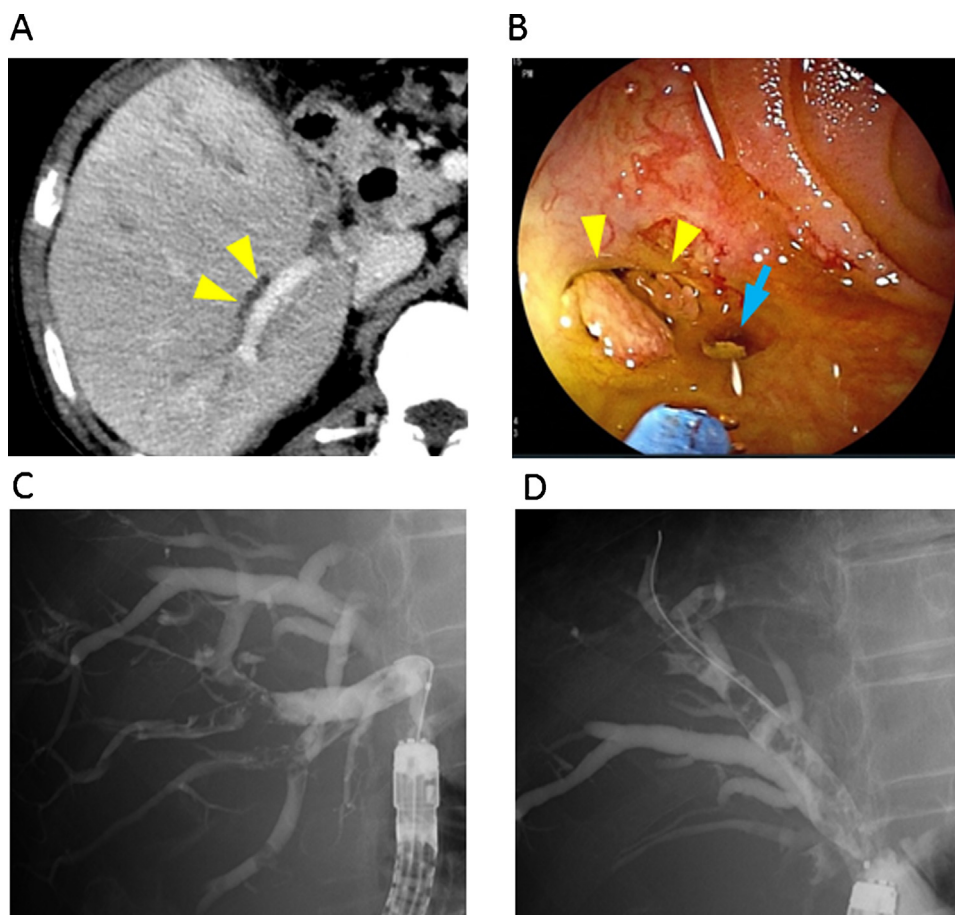


Fig. 3. (A) Postoperative CE-CT imaging study: Arrowheads indicate dilatation of the intrahepatic duct of the posterior segment. (B–D) Postoperative imaging studies using double-balloon enteroscopy (DBE): (B) Arrowheads and arrow indicate the papillary tumors protruding from the anastomotic orifice of hepatic duct of segment 6 (B6) and segment 7 (B7), respectively. DBE-assisted direct cholangiography indicates filling defects throughout B6 (C) and B7 (D).

much less aggravating tumor compared with ICC, and it may be relevant to consider liver transplantation for IPNB patients with multiple lesions.

In the present case, we experienced the diagnostic and therapeutic difficulties of remnant intrahepatic bile duct recurrence following major hepatectomy with biliary reconstruction. Postoperative work-up was periodically performed, including blood tests and abdominal CE-CT, with recurrence being recognized by DBE at 29 months after surgery. This patient had sustained repetitive cholangitis with increased biliary enzymes since the early postoperative period. These phenomena may indicate the presence of recurrence in the remnant intrahepatic bile duct at the early phase following surgery. Although CE-CT showed dilatation of the intrahepatic bile duct, it was difficult to detect recurrent tumor tissue in the remnant hepatic duct. Hence, periodical CT imaging may be insufficient in the present case. Recent technical advances in endoscopic interventions enable diagnostic and therapeutic ERC even in patients with altered gastrointestinal anatomies due to surgery [10]. Therefore in such cases, the use of DBE-assisted direct cholangiography should be considered at the early postoperative phase. This procedure not only allowed diagnosis of recurrence but contributed to improvement of the quality of life of this patient.

In conclusion, we experienced an IPNB case that would have been expected to have long-term survival because this was a case of early-stage adenocarcinoma with R0 resection. However, this case experienced relapse in the remnant intrahepatic bile duct approximately 2 years after surgery. This suggests that we should consider multicentric remnant intrahepatic bile duct recurrence in

IPNB patients with multiple lesions. Endoscopic approaches, such as DBE, may be useful in diagnosis of recurrence and palliation of symptoms in selected patients.

Conflict of interest

Narita and other co-authors have no conflict of interest.

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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 of this journal.

Author contribution

(1) Study conception and design; Narita, Ikai.(2) Drafting manuscript or critical revision of the manuscript; Narita, Ikai, Matsusue, Hata, Yamaguchi, Otani, Endo, and Mizumoto.(3) Final approval of the manuscript; Narita, Endo, Mizumoto, Matsusue, Hata, Yamaguchi, Otani, Ikai.

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