

Case Report

Clinical Features of Intraductal Papillary Neoplasm of the Bile Duct : Report of 3 Cases

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ABSTRACT

Intraductal papillary neoplasm of the bile duct (IPNB) is a rare tumor that is characterized by papillary growth into the bile duct lumen and is considered as a biliary counterpart of intraductal papillary mucinous neoplasm (IPMN) of the pancreas. However, the definition of IPNB remains controversial because its malignant potential is higher and its frequency of mucus production is lower than those of IPMN. Herein, we report 3 cases of IPNB resected at The Jikei University Daisan Hospital. Mucus production was detected in all cases, in which ovarian-like stroma was absent but bile duct communication was present. The 3 cases were of the pancreatobiliary subtype, the gastric subtype, or the oncocytic subtype. The histologic findings in all cases were cystadenocarcinoma. With curative resection all patients survived more than 3 years. In summary, curative resection improves survival for IPNB more than for ordinary cholangiocarcinoma. (Jikeikai Med J 2016 ; 63 : 31-6)

Key words : intraductal papillary neoplasm of bile duct, bile duct communication, ovarian-like stroma, classification of subtype

INTRODUCTION

Intraductal papillary neoplasm of the bile duct (IPNB) is a recently updated concept that was classified by the World Health Organization classification scheme revised in 2010 as a cystic tumor of the liver with mucinous epithelium. An IPNB is characterized by the absence of ovarian-like stroma and the presence of bile duct communication (BDC), unlike a mucinous cystic neoplasm. An IPNB can sometimes be accompanied by marked dilatation of the bile duct due to hypersecreted mucus. However, the definition of IPNB remains controversial because of clinicopathological differences from intraductal papillary mucinous neoplasm (IPMN). We describe the clinicopathological features

of 3 cases of IPNB.

CASE PRESENTATION

Case 1

A 76-year-old man with diabetes mellitus who had undergone hormonal therapy for prostate cancer was found with computed tomography (CT) performed at The Jikei University Daisan Hospital to have a multilocular cyst in the right lobe of the liver. Therefore, the patient was referred to the Department of Surgery for further examination and treatment. Contrast-enhanced CT revealed a multilocular cystic lesion, 70 mm in diameter, in the anterior segment of the liver (Fig. 1A). However, there was no evi-

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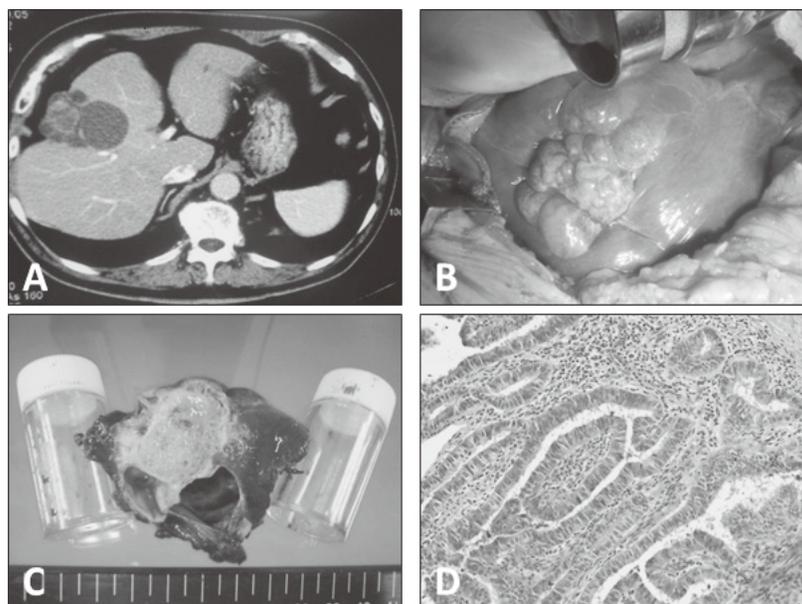


Fig. 1. Images and pathological findings of case 1.

- (A) Enhanced computed tomography exhibited a cystic lesion, 70 mm in diameter, in the anterior segment of the liver.
 (B) Intraoperative view showed a hard mass of 70 × 50 mm.
 (C) The content of the cystic lesion was abundant mucus.
 (D) Histopathological findings showed a tumor that was diagnosed as a low-grade cystadenocarcinoma with nuclear atypia. No ovarian-like stroma was identified (hematoxylin and eosin staining; magnification, × 20).

Table 1. Laboratory data of the patients

	Case 1	Case 2	Case 3
Aspartate aminotransferase (IU/l)	33	37	30
Alanine aminotransferase (IU/l)	25	60	46
Alkaline phosphatase (IU/ml)	260	1,141	599
Total bilirubin (mg/dl)	0.6	0.7	0.9
Direct bilirubin (mg/dl)	0.2	0.4	0.5
White blood cells (× 10 ³ /μl)	4.4	8.3	3.1
Hemoglobin (g/dl)	13.3	12.4	13.4
Platelets (× 10 ³ /μl)	169	319	151
Carcinoembryonic antigen (ng/ml)	1.8	1.9	4
Carbohydrate antigen 19-9 (U/ml)	32	66	27
Alpha-fetoprotein (ng/ml)	2	3	2
C-reactive protein (mg/dl)	0.1	0.1	0.3

dence of regional lymph node or distant metastasis. Serum levels of carcinoembryonic antigen and carbohydrate antigen (CA) 19-9 were within normal limits (Table 1). According to the preoperative diagnosis of mucinous cystadenocarcinoma, the patient underwent anterior segmentectomy. Macroscopic examination found that the cystic lesion, 90 mm in diameter (Fig. 1B), was multilocular and contained a large amount of mucus and a solid lesion (Fig. 1C). Pathologic examination showed a noninvasive cystadenocarcino-

ma, but ovarian-like stroma was not detected in the specimen. The BDC was pathologically proven without evidence of stromal invasion. Immunohistochemical analysis revealed that all neoplasm cells were negative for the proteins mucin (MUC) 1, MUC-2, MUC-5AC, and MUC-6. Both histological and immunohistochemical findings suggested that the tumor could be classified as the pancreatobiliary subtype, which is 1 of 4 different subtypes of IPNB (Fig. 1D). The patient has been free of recurrence for 5 years 8 months after the operation (Table 2).

Case 2

A 59-year-old man with diabetes mellitus went to a nearby hospital with a complaint of epigastralgia. Because abdominal ultrasonography showed a 50-mm-diameter cystic lesion in the left lobe of the liver, the patient was referred to The Jikei University Daisan Hospital for further evaluation. Laboratory studies showed slight elevation of the serum CA19-9 level (66 U/ml) (Table 1). Ultrasonography also showed a 60-mm-diameter hypoechoic lesion in the left lobe of the liver. In the same area contrast-enhanced CT revealed a 60-mm-diameter cystic lesion (Fig. 2A). Endoscopic retrograde cholangiography (ERC) showed

Table 2. Summary of our series

	Case 1	Case 2	Case 3
Sex	Male	Male	Male
Age (years)	76	69	72
Symptom	None	Epigastralgia	Epigastralgia
Tumor location	S5	S4	S4
Tumor size (mm)	79	70	70
Bile duct communication	+	+	+
Mucus production	+	+	+
Resection margin	-	-	-
Pathology	Cystadenocarcinoma Noninvasive	Cystadenocarcinoma Noninvasive	Cystadenocarcinoma Noninvasive
Subtype	Pancreatobiliary	Oncocytic	Gastric
Survival period (months)	68	63	41

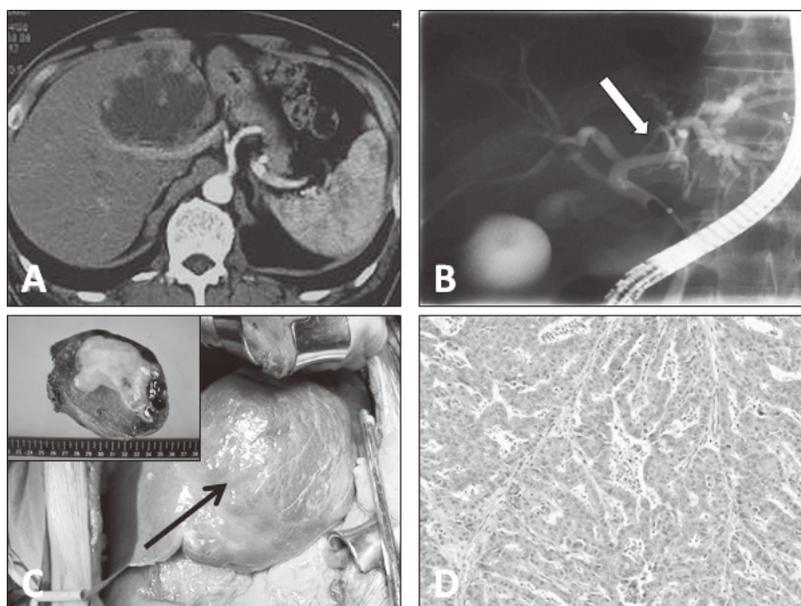


Fig. 2. Images and pathological findings of case 2.
 (A) Enhanced computed tomography showed a 60-mm-diameter cystic mass in the left hepatic lobe. There was no dilation of intrahepatic or extrahepatic bile ducts.
 (B) Endoscopic retrograde cholangiography showed an expanded papilla of Vater due to a mucous plug and the bile duct communication in the left lobe (arrow).
 (C) The gross appearance of the 70 × 60-mm tumor (arrow). The inner cavity of the resected specimen was filled with mucus.
 (D) Pathological diagnosis was cystadenocarcinoma. No stromal invasion or ovarian-like stroma was detected.

dilatation of the left intrahepatic bile duct and BDC (Fig. 2B). Because malignancy was suspected, extended left hepatectomy was performed. Histological examination indicated noninvasive cystadenocarcinoma without ovarian-like stroma. The resected specimen showed a large amount of mucus in the cystic lesion (Fig. 2C). Hematoxylin and eosin staining and immunostaining revealed neoplastic cells to be positive for MUC-1, MUC-5AC, and MUC-6 and negative

for MUC-2, and the oncocytic subtype of IPNB was diagnosed (Fig. 2D). The patient has been free of recurrence for 5 years 3 months postoperatively (Table 2).

Case 3

A 69-year-old man was referred to The Jikei University Daisan Hospital because of abdominal pain. Physical examination revealed mild tenderness in the upper abdomen.

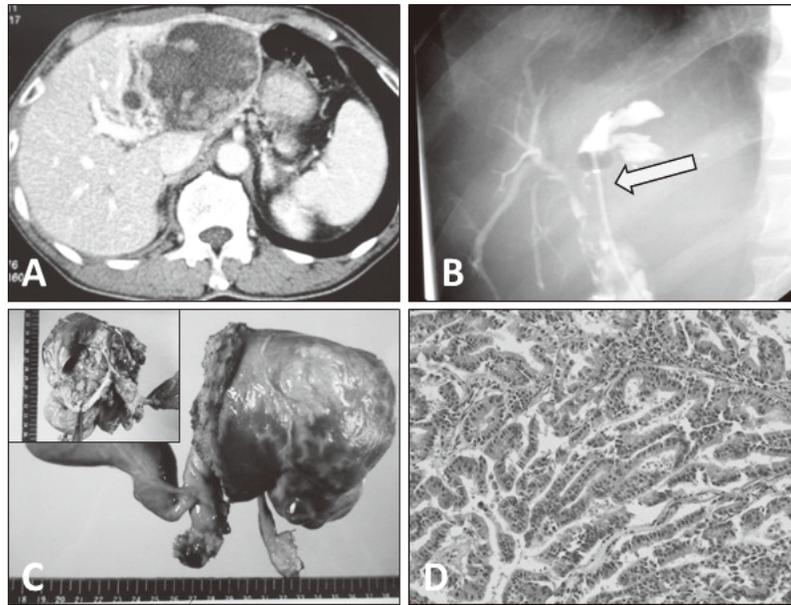


Fig. 3. Images and pathological findings of case 3.

- (A) Enhanced computed tomography exhibited a 70-mm-diameter cystic mass in the left hepatic lobe.
 (B) Endoscopic retrograde cholangiography revealed that the cystic mass in the left lobe of the liver was communicating with the bile duct (arrow).
 (C) Macroscopic findings of the resected specimen. The cystic lesion measured 80 × 50 mm and contained abundant mucus.
 (D) The pathological diagnosis was cystadenocarcinoma. The tumor was lined by low columnar epithelia with slight cellular atypia. No ovarian-like stroma was seen throughout the cyst walls.

Abdominal CT revealed a 90-mm-diameter cystic lesion in the left lobe of the liver (Fig. 3A). The ERC exhibited mucus secretion and BDC (Fig. 3B). Chemical examination of the serum revealed no elevation of hepatobiliary enzymes and a lack of inflammatory changes. Serum levels of CA19-9, and alpha-fetoprotein (AFP) were within normal limits (Table 1). Thus, IPNB was diagnosed in the left intrahepatic duct, and extended left hepatectomy was performed (Fig. 3C). The pathological diagnosis was noninvasive cystadenocarcinoma without apparent infiltration to the intrahepatic bile duct (Fig. 3D). Immunostaining showed neoplastic cells positive for MUC-1, MUC-5AC, and MUC-6 and negative for MUC-2. The gastric subtype of IPNB was diagnosed. The patient has been without recurrence for 3 years 5 months postoperatively (Table 2).

DISCUSSION

On the basis of the concept proposed by Nakanuma and colleagues¹⁻³, the World Health Organization Classification of Tumors in 2010 re-classified the disease entity “biliary cystadenoma and adenocarcinoma” as either mucinous cystic

neoplasm or IPNB, according to the presence of ovarian-like stroma and BDC⁴. An IPNB was widely considered to be a biliary counterpart of an IPMN owing to similar clinicopathological features. However, even though most IPMNs obtain the ability to produce mucus, hypersecretion is present in only 35.7% of patients with IPNB⁵. Moreover, the malignant potential of IPNB is perceived to be greater than that of IPMN^{5,6}. A recently reported liver cystic neoplasm with mucinous epithelium but without ovarian-like stroma or BDC was difficult to classify, on the basis of only histological findings, as a mucinous cystic neoplasm or IPNB⁷. Thus, whether IPNB is a counterpart of IPMN remains controversial, and the World Health Organization classification is entirely appropriate.

In regard to etiopathology, recent reports have proposed that peribiliary glands are the origin of IPNB and that a tumor derived from these glands extends into the epithelium^{8,9}. These reports have suggested that IPNB might also undergo a carcinogenesis process like that in the adenoma-carcinoma sequence theory.

An IPNB can be classified, on the basis of immunohistologic and morphologic findings, into 4 subtypes — gastric,

intestinal, pancreatobiliary, and oncocytic — similar to those of IPMN⁴. A study of 97 cases of IPNB found the following frequencies of subtypes: gastric, 15.5%; intestinal, 47.4%; pancreatobiliary, 34.0%; and oncocytic, 3.1%¹⁰. In contrast, the gastric subtype was most common for IPMN¹¹. According to several studies, in IPNB mucus hypersecretion is found at a rate of more than 50% in the large intrahepatic bile ducts^{3,5}. In the present series, the tumors were located in the liver. As noted earlier, unlike IPMN, IPNB develops invasive carcinoma at a high rate (61.1%)⁵. Moreover, the frequency of mucus hypersecretion is in inverse proportion to the frequency of invasive IPNB⁵. Interestingly, 77.1% of cases of the pancreatobiliary subtype were related to invasive IPNB⁵. Additionally, the pancreatobiliary subtype has been reported to be associated with non-mucus-producing IPNB, whereas the intestinal subtype was the most common subtype of mucus-producing IPNB¹². Mucus-producing IPNB has also been reported to be significantly related to the gastric or intestinal subtypes¹⁰. In the present study, 1 patient had the pancreatobiliary subtype, 1 had the gastric subtype, and 1 had the oncocytic subtype, but all were shown by pathological examination to have noninvasive adenocarcinoma. Clinical mucus production was observed in all cases. Therefore, our clinicopathological features of IPNB differ from those of previous reports.

Typical radiological features of IPNB consist of bile duct dilatation due to hypersecreting mucus and intraductal papillary growth nodules¹³. For preoperative diagnosis of IPNB, examinations useful for observing bile duct dilatation include ultrasonography, CT, magnetic resonance imaging (MRI), and ERC. Ultrasonography is clinically useful as an initial examination for demonstrating biliary dilatation and obstruction with viscous mucus¹³. In one study, ultrasonography, CT, and MRI could be used to detect intraductal nodules, although the sensitivity ranged from 41.2% to 97.0%¹⁴. On the other hand, ERC and intraoperative cholangiography were more efficient for detecting IPNB than were CT or MRI¹⁵. Furthermore, ERC remains effective for direct proof of mucus production as a filling defect in the bile duct. In addition, ERC is helpful in detecting BDC, in spite of its invasive nature¹⁶. In the present study, ERC revealed clinical mucus production and detected BDC in 2 cases.

For the assessment of superficial spread, transhepatic cholangioscopy was diagnostically useful because it allows biopsy to evaluate the extent of superficial spread¹⁷. How-

ever, pathologic diagnosis by means of biopsy is reportedly unable to reflect the actual stage because the foci might differ and because mixed pathologic findings might exist in the same lesion¹⁸. On the other hand, intraductal ultrasonography might be useful for locating the IPNB and assessing the depth of invasion¹⁹.

Regarding the treatment of IPNB, some reports have demonstrated that resected cases have a better prognosis than do cases of conventional cholangiocarcinoma^{20,21}. Therefore, for IPNB the treatment of first choice is surgical resection. In the present study, because all patients who had undergone curative resection have survived for more than 3 years, the surgical procedure was beneficial for them.

Patients with IPNB of the pancreatobiliary subtype have a significantly poorer prognosis than do patients with other subtypes⁵. The reported 5-year survival rate was highest among patients with the gastric subtype (83.9%) but was lower among patients with the intestinal (75.4%) or pancreatobiliary (46.8%) subtype⁸. Depending on the progression, the 5-year survival rate was 100% in patients who had IPNB and a noninvasive carcinoma⁸. In contrast, for patients with an invasive carcinoma, the 5-year survival rate was only 14%¹⁸. Therefore, we believe that evaluating the presence of mucus production and classifying the phenotype are crucial for determining the prognostic of IPNB. A recently published multicenter study of cases of mucin-producing IPNB in Japan has revealed that the subtypes were pancreatobiliary in 36.0%, intestinal in 27.7%, the oncocytic in 19.3%, and gastric in only 10.1%²². The mean 5-year survival rate of the 105 patients with mucin-producing IPNB was 84%²². These results suggest that most cases of IPNB have a putative mucus-phenotype association that improves the prognosis.

CONCLUSIONS

We have described 3 cases of IPNB. Curatively resected IPNB has a better prognosis than conventional cholangiocarcinoma. Important for curative resection is accurate assessment of the extent of superficial spread.

Authors have no conflict of interest.

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