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Original Article

Clinicopathological characterization of so-called "cholangiocarcinoma with intraductal papillary growth" with respect to "intraductal papillary neoplasm of bile duct (IPNB)"

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Abstract: Cholangiocarcinoma (CC) of the biliary tract occasionally presents a predominant intraductal papillary growth in the bile ducts, called as biliary tract carcinoma (BTC) of papillary growth (PG) and intrahepatic CC (ICC) of intraductal growth (IG) type. Recently, intraductal papillary neoplasm of bile duct (IPNB) has been proposed as a pre-invasive biliary neoplasm. This study was performed to characterize pathologically BTC of PG type and ICC of IG type with respect to IPNB. It was found that 126 of such 154 CCs (81.8%) fulfilled the criteria of IPNB, while the remaining 28 cases showed different histologies, such as tubular adenocarcinoma and carcinosarcoma. These IPNBs occurred in old aged patients with a male predominance, and the left lobe was rather frequently affected in the liver. A majority of these cases were high grade IPNB (43 cases) and invasive IPNB (77 cases), while low grade IPNB was rare (6 cases). Pancreatobiliary type was predominant (48 cases) followed by gastric (30 cases), intestinal (29 cases) and oncocytic (19 cases) types. Mucus hypersecretion was found in 45 cases, and this was frequent in IPNB at the intrahepatic large bile duct and hilar bile ducts but rare at the extrahepatic bile ducts. Interestingly, 36 cases of high grade and invasive IPNBs contained foci of moderately differentiated adenocacinoma within the intraductal papillary tumor. In conclusion, a majority of ICC of IG type and BTC of PG type could be regarded as a IPNB lineage, and clinically detectable IPNBs were already a malignant papillary lesion.

Keywords: Biliary tree, intraductal papillary neoplasm, intraductal cholangiocarcinoma, papillary cholangiocarcinoma, phenotype

Introduction

Cholangiocarcinomas (CCs) of the intrahepatic large bile ducts and biliary tract including hilar bile ducts usually present with a nodular and/or sclerosing type, while some of these CCs present predominantly intraductal or papillary growth pattern in the dilated bile ducts [1-6]. Such cases have been called intrahepatic CC (ICC) of intraductal growth (IG) type or biliary tract carcinoma (BTC) of papillary growth (PG) type [1-6]. These cases are known to have characteristic clinicopathological fatures [2, 7-9]: they are not infrequently associated with mucus hypersecretion (mucus secreting bile duct tumor), and present a rather favorable prognosis after surgical resection in comparison with other gross types of CCs [13, 14], and hepatolithiasis is one of risk factors [8]. Histologically, they were well-differentiated adenocarcinoma and were frequently positive for CDX2 and MUC2 [8]. Recently, as an early neoplastic or

pre-invasive malignant lesion of CC, two types of neoplastic lesions have been proposed: intraepithelial biliary neoplasm (BilIN) and intraductal papillary neoplasm of bile duct (IPNB) [1, 10, 11]. The former is a flat, microscopic lesion, while the latter is a grossly visible lesion showing mainly intraductal papillary neoplasm. The latter resembles pathologically and also phenotypically "intraductal papillary mucinous neoplasm of pancreas (IPMN)" of pancreas, particularly the main pancreatic duct type [1, 10]. Interestingly, both IPMN and IPNB are known to present four phenotypes: pancreatobiliary, gastric, intestinal and oncocytic types. While IPNB is basically a pre-invasive neoplastic biliary lesion in the duct lumen, quite often it accompanies with periductal invasive adenocarcinoma and such cases are called invasive IPNB [10, 12-14]. While IPNB had been originally reported in the cases with hepatolithiasis [15], it was then recognized in cases without hepatolithaisis, too [10]. While ICC of IG type and BTC of PG type appear to share many common features of IPNB and both seem to be overlapped pathological entities, there have been no systematic studies on the relation between two entities, so far, and there might have therefore been some confusions in these entities, clinically.

To address this important issue in practical fields, we tried to characterize pathologically ICC of IG type and BTC of PG type with reference to IPNB. Particularly, we tried to know whether ICC of IG type and BTC of PG type were actually IPNB itself or not. For this purpose, a total of 154 surgically resected cases were collected from five hospitals in Japan, and these cases were originally diagnosed as ICC of IG type and BTC of PG type in individual hospitals. These cases were examined pathologically with respect to the histologic grades, structural atypia and complexity, mucus hypersecretion, and phenotypes of the intraductal papillary lesion with respect to IPNB. The number of such biliary tumor cases examined was the largest in this type of study, so far.

Materials and methods

Case selection and tissue preparation

One hundred fifty-four cases of CCs which were diagnosed as ICC of IG type or BTC of PG type in National Cancer Center Central Hospital (43 cases), Kyushu University Hospital (18 cases), Tokyo's women College Hospital (51 cases), Tohoku University Hospital (36 cases) and Kanazawa University Hospital (6 cases) were available for histologic observation in this study. All of these cases were filed in the computer system in individual hospitals while the duration of such file was variable. The introduction of such computer system was variable in these hospitals. CCs of left or right hepatic ducts and their convergence were included in BTC in this study, though their exact location in the hilar regions could be controversial in many cases. Sufficient clinical and laboratory data including mucin hypersecretion and the data and findings at surgical operation(s) were available in all of these 154 cases. Mucus hypersection from the biliary tumor was defined as mucin excretion into the duodenum via Papilla Vater and/or as grossly visible mucin in the dilated bile ducts at surgical operation. All of these cases were surgically resected cases, and the cases who underwent at least gross total resection were only included. More than 3 tissue specimens including main tumor(s) were prepared, and they were fixed in 10% buffered formalin and embedded in paraffin. More than 3 thin sections from these paraffin blocks were processed for routine histologic processes including H&E and mucin stainings. In a majority of cases, several sections were processed for immunostaining of MUC2 (intestinal mucin), MUC5AC (gastric, pancreatobiliary and intestinal mucin), MUC6 (gastric mucin) and/or CK20 (intestinal marker) for phenotyping of neoplastic epithelial cells in variable combinations.

One pathologist (Y.N.) visited to these hospitals and examined the routinely processed sections of these cases with a help of immunostainings, gross pictures preserved and clinical informations, and discussed with clinician and/or pathologist(s) of individual hospitals. Then, the following clinicopathological data and findings were recorded and evaluvated. This study was approved by Ethic Committee of Kanazawa University Graduate School of Medicine.

Definition of IPNB

According to previous reports [1, 10, 12-14, 16], IPNB was defined pathologically by using the following inclusion and exclusion criteria [1, 10], and the cases fulfilled these criteria were regarded as IPNB in this study.

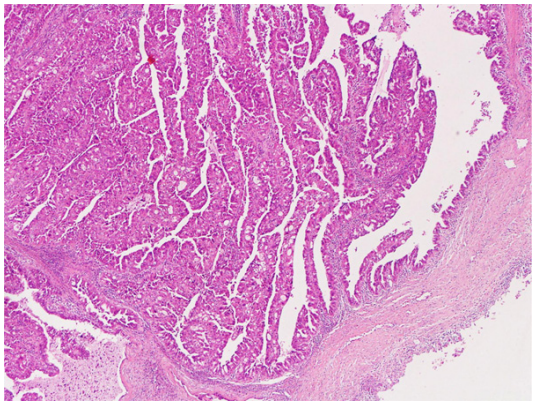

Figure 1. Intraductal papillary neoplasm of the intrahepatic large bile duct of the left lobe. HE., x30.

Inclusion criteria: i) the biliary tumor(s) showing intraluminal protruding mass or cast-like lesion(s) or papillary intraluminal papillary growth (**Figure 1**). ii) the affected bile ducts by the tumor are variably dilated, and some showed cystic dilatation. iii) the tumor(s) are histologically mainly well differentiated papillary adenocarcinoma and/or papillary epithelial borderline lesion or adenoma with fine fibrovascular stroma. Biliary neoplasm(s) containing small foci of tubular component among the predominant papillary lesions are included. iv) the tumor showing either one or several of phenotypes of "intestinal", "gastric (foveolar and pyloric)", "pancreatobiliary" and "oncocytic" epithelia (**Figure 2**), all of four types being reported also in the pancreatic IPMN. The IPNB cases with variable foci of well to moderately differentiated adenocarcinoma different from typical IPNB with either of four phenotypes, were also included, if IPNB components were clearly present in the intraductal papillary tumor.

Exclusion criteria: i) borderline or carcinoma composing of considerable tubulo-papillary or tubular components protruding the bile duct lumen was excluded. ii) moderately to poorly differentiated adenocarcinoma with no evidence of differentiation to the above-mentioned four phenotypes of IPNB occupying the intraductal tumor in the dilated bile duct, were excluded. iii) mucinous cystic neoplasm with ovarian-like stroma of the liver or biliary tract was excluded. iii) other types of malignant tumors including small or large cell carcinoma, hepatocellular carcinoma (HCC), combined hepatocellular cholangiocarcinoma (cHC-CC), carcinosarcoma, and sarcoma of any type showing intraductal growth were excluded. iv) reactive or hyperplastic biliary epithelial lesions were also excluded.

Pathological studies

The following pathologic features were mainly examined in routinely processed histologic sections with a help of immunosainings and also in consideration of gross pictures and other clinical data. The location of IPNB was determined by its main location along the biliary tree, and divided into the intrahepatic large bile duct (right lobe, left lobe and caudate lobe), hilar bile duct (right and left bile duct and its convergence) and extrahepatic bile duct excluding the hilar bile duct. In this study, the tumors of the gallbladder and ampulla of Vater were not included.

Histologic grades of IPNB: They were classified into three categories (4): i) low grade IPNB, ii) high grade IPNB, and iii) invasive IPNB. Low grade IPNB presents so called low grade biliary epithelial dysplasia or borderline lesion and cellular and nuclear atyica are mild, and so-called papillary adenoma or biliary papilloma or papillomatosis were included in this category. High grade IPNB is non-invasive or in situ papillary adenocarcinoma with fine fibro-vascular connective tissue and show cellular/nuclear and structural atypia enough for malignancy. Invasive IPNB is IPNB with evident invasion of carcinoma cells to the bile duct wall and/or the surrounding structures including liver parenchyma and also pancreas, and show basically papillary adenocarcinoma and show cellular/nuclear and structural atypia within the intraductal papillary tumor, similar to high grade IPNB. When the invasion into the duct wall and periductal tissue was suspicious and not evident, such cases were included in high grade IPNB.

Invasive IPNB was further divided into minimal (microscopically identifiable) invasive type and grossly visible invasion. The former was confirmed mainly at the invasion to the bile duct wall and periductal tissue, and the latter showed grossly visible invasion to the periductal tissue, including the surrounding structures such as the periductal connective tissue, liver parenchymal and pancreas. Some of the latter could be grossly described as mass or nodule formation or thickening of affected bile duct(s).

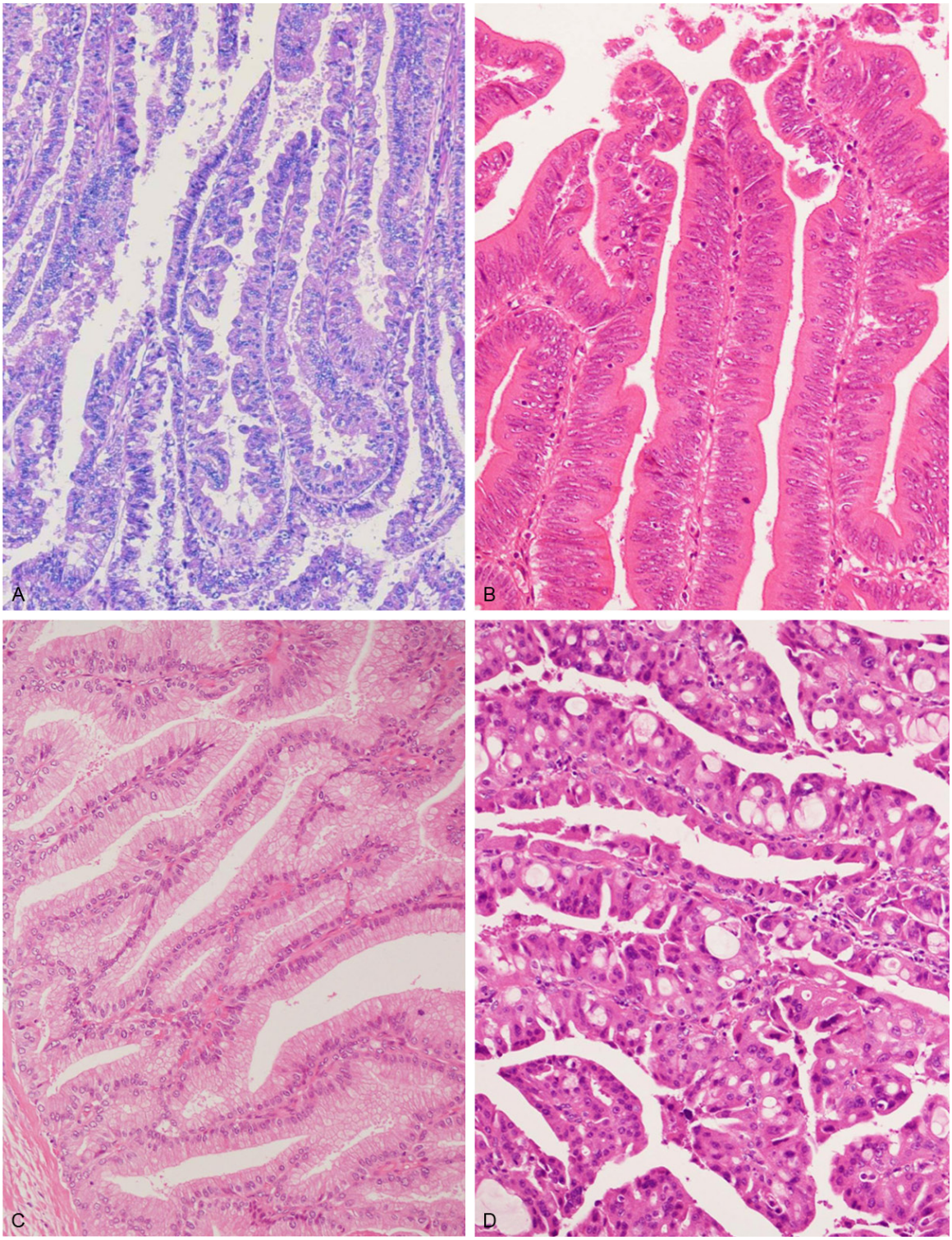

Figure 2. Four phenotypes of intraductal papillary neoplasm of bile duct. A. Pancretobiliary type. HE., x70. B. Intestinal type, HE., x100. C. Gastric type, HE., x100. D. Oncocytic type, HE., x150.

Phenotypes: Neoplastic epithelia of IPNB was histologically classified into four phenotypes with a help of immunostainings [1, 10]: i) pancreatobiliary type characterized by cuboidal to short columnar cells with pale eosinophilic or amphophilic cytoplasm and round nuclei

Table 1. Main clinicopathological features of 126 cases of IPNB

Age (years)	67.2 ± 10.1 (range: 35-89)
Sex (male : female)	82 : 44
Main location of IPNB	
ILBD, of left lobe	48 cases (38.1%[b])
ILBD, of right lobe	16 cases (12.7%)
ILBD, of caudate lobe	8 cases (6.3%)
Hilar bile ducts	15 cases (11.9%)
Biliary tract[a]	39 cases (31.0%)
Mucus hypersecretion	45 cases (35.7%[c])

IPNB, intraductal papillary neoplasm of bile duct; ILBD, intrahepatic large bile ducts; [a]excluding hilar bile duct; [b]percentage of cases according to the location of IPNB along the biliary tree; [c]percent of positive case.

(**Figure 2A**), ii) intestinal type characterized by stratified tall columnar cells with goblet cells, resembling the intestinal epithelia (**Figure 2B**), iii) gastric type characterized by columnar cells with abundant cytoplasmic mucin, some being remniscent of gastric foveolar epithelium, and the other resembling pyloric-like glands and by combined two subtypes (foveola type and pyloric gland type) (**Figure 2C**), and iv) oncocytic type characterized by an abundant eosinophilic cytoplasm and enlarged round nuclei (**Figure 2D**). Phenotyping was done according to our previous studies [3, 4] and also by considering the phenotypes of pancreatic IPMN which is also known to present either of these four phentoypes [16]. Goblet cells are also occasionally found in the gastric type. CK20 and MUC2 expression was common in the intestinal type, MUC6 in the gastric type and oncocytic type, while MUC5AC was expressed in either of four phenotypes, and not specific to each phenotype. When more than one phenotypes were identifiable in the IPNB lesion, the most predominant phenotype was regarded as the phenotype in such cases.

Luminal lateral spread: This is characterized by intraepithelial continuous spread of neoplastic cells to the surrounding bile ducts from IPNB, and is divided into i) minimal or local spread, ii) moderate spread and iii) extensive spread type. While the majority of lateral spread shows the replacement of the lining epithelia of bile ducts by neoplastic cells, the mucosa propria-like structure by neoplastic cells is occasionally seen. In i), the luminal lateral spread is confined to just the surrounding bile ducts to IPNB, while in iii) luminal spread is extensively seen in the extrahepatic and/or hilar bile ducts and/or intrahepatic bile ducts including the ones adjacent to the IPNB. The last showed neoplastic biliary lesion replacing continuously the lining epithelia of the surrounding bile duct and also in the septal or interlobular bile ducts in the portal tracts in the liver parenchyma. The extent of ii) is between i) and iii). Neoplastic cells also spread intraepithelially into the peribiliary glands of the hilar regions and also of the extrahepatic bile ducts.

Statistical analysis

Intergroup comparisons were made using the Spearman's correlation test and the chi-square test. The results were considered significant if the *P* value was < 0.05.

Results

Main clinicopathological features

One hundred twenty-six of 154 cases (81.8%) of ICC of IG type and/or BTC of PG type fulfilled the inclusion and exclusion criteria of IPNB, and the remaining 28 cases who failed to fulfill these criteria were classifiable as follows: 3 cases of predominantly tubular adenocarcinoma, 15 cases of moderately to poorly differentiated adenocarcinoma without typical papillary features or phenotypes of IPNB, one case of carcinosarcoma, 3 cases combined HC-CC showing intraductal growth of CC components, 2 cases of multicystic carcinoma without ovarian like stroma showing intraductal growth, one case of giant mucinous carcinoma with focal intraductal growth, and 3 cases of diffuse mucosal spread of in situ carcinoma without grossly visible papillary features.

The main clinicopathological features of 126 cases of IPNB are shown in **Table 1**. Their age ranged from 35 yrs to 88 years with an average of 67.2 years. They were composed of 82 males and 44 females. IPNB was mainly located at the intrahepatic large bile ducts of left lobe (48 cases), at those of right lobe (16 cases) and at those of caudate lobe (8 cases), and the biliary tract including the hilar bile ducts (54 cases). In the latter, IPNB was mainly located in the hilar bile duct (15 cases) and in the other parts of biliary tract excluding the gallbladder (39 cases). Interestingly, 45 of 126 cases were recorded clinically as mucus hypersecreting

Table 2. Histologic grades of IPNB and other pathologic factors

	Low grade IPNB	High grade IPNB	Invasive IPNB		
			total	minimal[a]	grossly[a]
Number of cases	6 (4.8%[b])	43 (34.1%)	77 (61.1%)	50	27
Phenotypes					
PB type	0[c]	12	36	22	14
Intestinal type	2	10	17	9	8
Gastric type	4	12	14	12	2
Oncocytic type	0	9	10	7	3
Mucus hypersecretion*	4	21	20	13	7
Foci of de-differentiation[d,*]	0	4	32	20	12
Luminal spread					
Limited	4	18	27	16	11
Moderate	1	11	27	19	8
Extensive	1	14	23	15	8

IPNB, intraductal papillary neoplasm of bile duct; PB type, pancreatobiliary type; [a]degree of ductal and periductal invasion; [b]proportion of IPNB cases according to histologic grade; [c]number of cases; [d]moderately differential adenocarcinoma; *$P < 0.01$ (Spearman's correlation test).

tumors, and in fact, much was shown in the tumor and/or in the affected bile duct lumen at the time of operation: mucus hypersecretion was found in IPNBs mainly involving the intrahepatic large bile ducts of the right, left and caudate lobe (38 of 72 cases, 52.8%), those involving the hilar bile duct (6 of 15 cases, 40%), though it was found only in 1 of 39 cases (2.6%) mainly involving the biliary tract excluding the hilar bile duct. As for the background lesions, 4 cases were associated with hepatolithiasis, 1 cases with chronic advanced liver diseases due to chronic viral hepatitis B, one case with primary sclerosing cholangitis (PSC), two cases with congenital hepatic fibrosis and Caroli's disease, and one case with congenital choledochal cyst. Interestingly, 6 of 126 cases with IPNB were under 50 years, and one of them was associated with PSC, while other 5 cases did not show specific hepatobiliary diseases.

Histologic featuers of IPNB

Histologic grades and invasion: As shown in **Table 2**, 6 cases were classified as low grade IPNB, 43 cases as high grade IPNB (**Figure 1**), and 70 cases as invasive IPNB. Among 77 cases of invasive IPNB, 50 cases showed focal or microscopic invasion and the remaining 27 cases showed a grossly visible invasion as a form of nodular or massive growth around IPNB. Invasive parts showed less differentiation and showed mainly tubular adenocarcinoma in comparison with IPNB itself, and mucinous change were focally found not infrequently at the beginning site of invasion. One case showed extensive mucinous carcinoma at the invasive areas.

As for the clinical features, there were no difference in sex and age distribution among these three groups. As for the mucus hypersecretion, it was found in 4 of 6 cases (66.7%) of low grade IPNB, 21 of 43 cases (48.8%) of high grade IPNB, 20 of 77 cases (25.9%) of invasive IPNB (13 of 50 microinvasive cases (26%) and 7 of 27 cases (25.9%) of grossly visible invasive cases). Mucus hypersecretion was decreased along with the progression of IPNB ($P < 0.01$).

Phenotypes: As shown in **Table 3**, the PB type was predominant in 48 cases of 126 cases (23.8%), the intestinal type was predominant in 19 cases (23.0%), the gastric type was predominant in 30cases (18.2%) and the oncocytic type was predominant in 13 cases (15.1%). While 6 cases of low grade IPNB were composed of two cases with intestinal type and 4 cases with gastric type, all of PB and onocytic type belong to high grade and invasive IPNB. As for the relation to mucin hypersecretion, it was found in 12 of 29 cases (41.3%) with the intestinal type, in 16 of 30 cases (53.3%) with the gastric type, in 12 of 48 cases (25.0%) with the PB type, and in 4 of 19 cases (21.0%) with the oncocytic types. Thus, the gastric and intestinal types were more frequently associated with mucus hypersecretion in comparison with the oncytic type and the PB type. As for the invasion and phenotypes, 6 low grade cases were composed of 2 cases of intestinal phenotype and four cases of gastric phenotype. Invasive type was found in 36 of 48 cases (75.0%) of PB type, in 17 of 29 cases (58.6%) of intestinal

Table 3. Phenotypes of IPNB and other histologic factors

	Pancreatobiliary type	Intestinal type	Gastric type	Oncocytic type
Number of cases	48 (38.1%[a])	29 (23.0%)	30 (23.8%)	19 (15.1%)
Histologic grades				
Low grade	0	2	4	0
High grade	12	10	12	9
Invasive	36	17	14	10
minimal	22	9	12	7
grossly	14	8	2	3
Mucus hypersecretion	12 (25.0%[b])	12 (41.3%)	16 (53.3%)	4 (21.0%)
Foci of de-differentiation	17 (35.4%[c])	10 (34.5%)	4 (13.3%)	5 (26.3%)
Intraluminal spread				
Limited	21	8	15	5
Moderate	11	9	10	9
Extensive	16	12	5	5

IPNB, intraductal papillary neoplasm of bile duct; [a]proportion(%) of cases according to predominant phenotype of IPNB; [b]percentage of positive cases in each phenotype; [c]percentage of positive cases in each phenotype.

type, 14 of 30 cases (46.7%) of gastric type, and 8 of 13 cases (52.6%) of oncocytic type. Particularly, a grossly visible invasion was found in 29.2% of PB type and 27.6% of intestinal type and 15.8% of oncocytic type, while such invasion was found in only 6.7% of gastric type.

Histologic heterogeneity: While low grade IPNB showed rather homogeneous structures and phenotypes, high grade and invasive IPNB frequently show considerable degree of structural atypia and more than one phenotypes. While 90 of 126 cases of IPNB were almost entirely composed of rather differentiated papillary carcinoma, the remaining 36 cases contained variable foci of moderately differentiated adenocarcinoma (**Figure 3B**) different histologically from IPNB with either of four phenotypes within the intraductal papillary tumor. The latter lesions were regarded to reflect the occurrence of de-differentiated carcinomas or neoplastic heterogeneity in IPNB lesions. This was frequent in PB type (17 of 48 cases, 35.4%) and intestinal type (10 of 29 cases, 34.5%) and oncocytic type (5 of 19 cases, 26.3%), while this was infrequent in the gastric type (4 of 30 cases, 13.3%). This was found in 4 of 43 cases (9.3%) of high grade IPNB, 32 of 77 cases (41.6%) of invasive IPNB (20 of 50 cases (40.0%) of microinvasion and 12 of 27 cases (44.4%) of grossly visible invasion), while this was not found in low grade IPNB. This feature was increased along with the progression of IPNB ($P < 0.01$).

Intrauminal lateral spread

Forty-nine cases showed limited superficial spread (benign or malignant), 39 cases showed considerable lateral spread, and the remaining 38 cases extensive spread. Interestingly, 26 cases showed intraepithelial spread into the peribiliary glands and their conduits, variably. As for the relation of the intraluminal lateral spread to the histologic grades and phenotypes, low grade type tended to show the limited spread. Otherwise, there were no evident correlations between them (**Tables 2** and **3**).

Discussion

The data obtained in this study are summarized as follows: i) a majority of ICC of IG type and/or BTC of PG type fulfilled the criteria of IPNB, though there were other malignant neoplasms presenting similar gross type. ii) As for histologic grades, a majority of these cases were high grade IPNB (43 cases) and invasive IPNB (77 cases), while low grade IPNB was rare (only 6 cases). Mucin hypersecretion was common in IPNB involving the intrahepatic large bile ducts and hilar bile ducts but rare in the biliary tract excluding the hilar bile ducts. Interestingly, 36 of 126 cases of IPNB contained foci of variable amount of moderately differentiated adenocarcinoma different from typical IPNB, suggesting development of dedifferentiation within the intraductal papillary tumor. iii) As for the phenotype, hepatobiliary type was predominant in 48 cases, intestinal type in 29 cases, gastric type in 30 cases, and oncocytic type in 19 cases. iv) 39 and 38 cases of IPNB showed moderate and extensive intraluminal lateral spread, respectively. A majority of CCs diagnosed as ICC of IG type and BTC of PG type could be regarded as a IPNB series, and these cases are

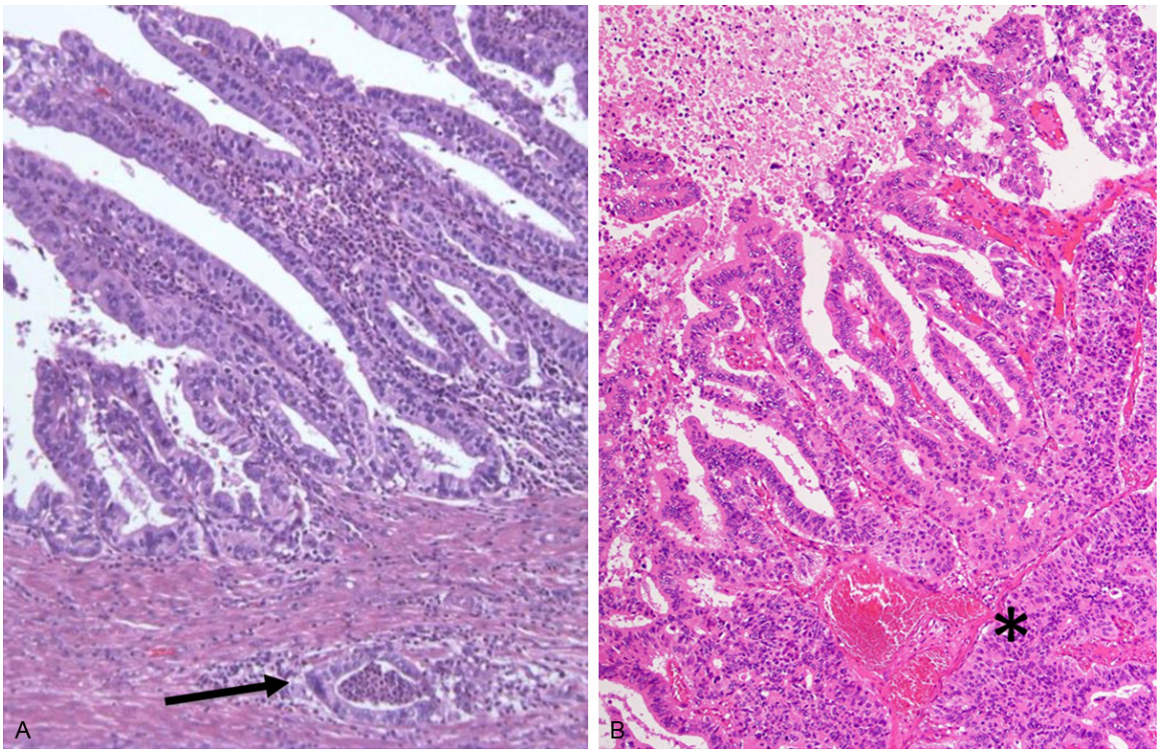

Figure 3. A. Focal and microinvasion (arrow) in intraductal papillary neoplasm of bile duct. HE., x70. B. Foci of moderately differentiated adenocarcinoma in intraductal papillary neoplasm of bile duct. HE., x70.

recommended to be studied clinicopathologically and treated therapeutically from the standpoint of IPNB.

It was found in this study that 126 of 154 cases of ICC of IG type and/or BTC of PG type fulfilled the inclusion and exclusion criteria of IPNB including invasive IPNB. However, the remaining 24 cases, all of which were diagnosed as ICC of IG type or TBC of PG type in individual hospitals, were different from IPNB, and they showed poorly differentiated adenocarcinoma, tubular adenocarcinoma, carcinosarcoma, cholangiocarcinoma component of combined HC-CC, and other malignant neoplasms. So, it is important practically that there were IPNB and also non-IPNB neoplasm in the cases of ICC of IG type and/or in those of BTC of PG type, and differential diagnosis should be carefully done between them clinicopathologically.

Analysis of the cases fulfilling IPNB disclosed that they were old aged with a male predominance, and the intrahepatic large bile ducts, the hilar bile ducts, and the extrahepatic bile duct were affected. Within the liver, the left lobe was preferentially affected, and interestingly, 8 of 72 cases of IPNB in the liver affected the caudate lobe. Furthermore, more than 35% of IPNB cases showed mucin hypersecretion which was common in IPNBs involving the intrahepatic large bile ducts and hilar bile ducts but rare in the biliary tract excluding the hilar bile ducts. These characters of IPNB cases were almost similar or identical clinicopathologically to those of ICC of IG type or BCT of PG type [2, 3, 8, 9, 17]. Hepatolithiasis was reported as one of risks associated with ICC of IG type [8, 15], and this disease was also found in 4 cases in this study. There are several reports that ICC of IG type or BCT of PG type showed a favorable prognosis in comparison with other types of ICC or BCT [8, 9, 17], and IPNB also reportedly presents such a favorable prognosis after surgical resection [2, 12, 13, 18]. These data support the above-mentioned conclusion that a majority of ICC of IG type or BCT of PG type were IPNB. Unfortunately, such prognostic studies after surgery have not been evaluated in this multi-institutional study.

It was found in this study that low grade IPNB was rather rare, and a majority of IPNB cases were high grade IPNB (43 cases) and invasive

IPNB (77 cases) with minimal and considerable invasion. It is well known that majority of IPMN of main-duct type are also already malignant at the time of diagnosis, and this character is in sharp contrast with branch-type IPMN of pancreas, the majoriy of which are low grade at the time of diagnosis [19]. There have been several studies that IPNB shares many features with main-duct type of IPMN but not branch-type IPMN [10, 11, 15], and it was found in this study that a majoriy of clinically detectable IPNB were already malignant, being pre-invasive or invasive variably, as in the main-duct type IPMN. This unique feature of IPNB seems to be confirmed by this study using many IPNB cases obtained from cases diagnosed as ICC of IG type or BTC of PG type. More studies are mandatory to clarify this unique aspect and progression of IPNB.

Invasive IPNB was further subdivided into minimal inasive and grossly invasive IPNB. Among 77 cases of invasive IPNB, 50 cases showed showed focal or microscopic invasion into the ductal wall and periductal tissue, and the remaining 27 cases showed a grossly visible invasion as a form of nodular or massive growth around IPNB. Invasive parts showed mainly tubular adenocarcinoma with or without micropaillary configurations and with stromal reactions including fibrosis as seen in ordinary ICC or BTC, and mucinous change was not infrequently found at the site of invasion. One case showed extensive mucinous carcinoma at the invasive areas. Frequent occurrence of such mucinous changes has already reported in invasive IPNB [1, 8, 10, 11, 20]. Exact incidence of progression of IPNB was confirmed first by this study. The degree of invasion is reported to have a great impact on the prognosis after surgical resection of IPNB [12, 21].

It was found in this study that IPNB cases of hepatobiliary type was most common (38.1%) followed by gastric type (23.8%), intestinal type (23%) and oncocytic type (15.1%). Several studies on IPNB showed that IPNB tended to show more than one phenotypes within the intraductal papillary tumor [10, 11], and this composite features of phenotypes was also found in this series, and the predominant phenotype was regarded as the one representing of each case. Such four phenotypes of IPNB are also reported in pancreatic IPMN, and the proportion of four phenotypes in IPNBs in this series was more or less similar to that of IPMN of main pancreatic duct type rather than that of branch type [17, 21, 22]. While 6 cases of low grade IPNB were composed of two cases with intestinal and four cases with gastric type, all of PB and onocytic type belong to high grade IPNB and invasive IPNB. As for the relation to mucin hypersection, it was common in the gastric type (53.3%) followed by the intestinal type (41.3%), the PB type (25.0%) and the oncocytic type (21.0%). As for the invasion and phenotypes, invasive IPNB was common in the PB type (75.0%) followed by the intestinal (58.6%) and oncocytic type (52.6%). Interestingly, 14 of 30 cases (46.7%) of gastric type belonged to the invasive IPNB. Interestingly, a grossly visible invasion was found in 29.2% of the PB type and 27.6% of the intestinal type and 15.8% of the oncocytic type, while such invasion was found in only 6.7% of the gastric type. Taken together, it seems plausible that the gastric type is less aggressive behavior and the PB type is more aggressive behavior with respect to the phenotypes of IPNB.

While IPNBs typically show well-differentiated papillary neoplasm with the fine fibrovascular stalk, they often show considerable degree of structural atypia and complexity [12, 14]. As mentioned above, a majority of clinically detectable IPNB was already malignant and not infrequently showed variable invasion. However, the exact histologic progression within the intraductal papillary tumor itself remains to be clarified. It was found in this study that in 90 of 126 IPNB cases, almost all intraluminal papillary neoplastic lesions were composed of rather typical IPNB components. However, the remaining 36 IPNB cases were found to contain variable foci of moderately differentiated adenocarcinoma different from typical papillary structures of IPNB, suggesting that such IPNB cases might have undergone dedifferentiation within the intraductal papillary tumors. This dedifferentiation was relatively common in the PB type (35.4%), the intestinal type (34.5%) in comparison with the gastric type (13.3%). Such lesion was found in 26.3% of the oncocytic type. Furthermore, this de-differentiation was common in invasive IPNB (41.6%), particularly in those with grossly visible invasion, in comparison with high grade IPNB (9.3%) and low grade IPNB (0%). It seems conceivable that dedifferentiation within the intraductal papillary tumor closely relates to the occurrence of inva-

sion of IPNB and this de-differentiation is likely to occur in the PB type.

Biliary neoplasms including CC and IPNB arising in intrahepatic large bile ducts and extrahepatic bile ducts is known to show lateral superficial spread [2, 7], and in this series, 49 cases showed limited superficial spread (benign or malignant), 39 cases showed considerable lateral spread, and the remaining 38 cases extensive spread. This lateral spread was rather limited in low grade IPNB in comparison with high grade IPNB and invasive IPNB, and was rather widespread in the intestinal phenotype. Interestingly, intraepithelial involvement of the peribiliary glands was also shown in 40 cases, suggesting that this type of spreading route is operative in IPNB as seen in CC [23].

In conclusion, a majority of CCs diagnosed as ICC of IG type of ICC and BTC of PG type were found to belong to an IPNB lineage, while a minority of them showed other types of malignant tumors. A majority of IPNB were high grade IPNB and invasive IPNB, while low grade IPNB was rare. Foci of moderately differentiated adenocarcinoma different from IPNB within the intradutal papillary tumor were not infrequently found in invasive IPNB, reflecting occurrence of such de-differentiation relates to the invasion. The PB type was associated with more malignant behavior while the gastric type with less malignant biologic behaviors. More studies are mandatory to clarify tumorigenesis and progression of this unique biliary papillary tumor.

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Disclosure of conflict of interest

None.

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