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Review

Biliary papillary neoplasm of the liver

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Summary. Biliary papillary neoplasia of the liver characterized by intraductal papillary growth of neoplastic biliary epithelia with a fine fibrovascular stalk has been sporadically reported, and includes intraductal growing cholangiocarcinoma and biliary papillomatosis. In addition, biliary papillary dysplasia and *in situ* and microinvasive carcinoma with papillary configuration reported in hepatolithiasis and in other chronic biliary diseases, could be included in this category. Usually, they arise in the intrahepatic large bile ducts, and the neoplastic and non-neoplastic parts of the intrahepatic biliary tree show saccular and segmental dilatation with mucin hypersecretion. This neoplasia frequently shows intraductal spreading and peribiliary glandular involvement. Acute repeated episodes of cholangitis or obstructive jaundice are a frequent clinical manifestation. Gastroenteric metaplasia with aberrant expression of cytokeratin 20, MUC2, MUC5AC, and/or MUC6, is frequent in the neoplastic parts, and biliary epithelial dysplasia with such metaplasia may give rise to *in situ* and then invasive carcinoma in hepatolithiasis. Interestingly, this type tends to contain foci of mucinous carcinoma elements, and this element may be predominant (mucinous carcinoma). Some may progress to "mucinous biliary cystadenocarcinoma" without ovarian mesenchymal stroma and with intraluminal continuous growth into the neighboring bile duct lumens. Interestingly, the biliary papillary neoplasm resembles histologically, phenotypically and clinically intraductal papillary mucinous neoplasm of the pancreas which is now being established as an infrequent, slow-growing pancreatic neoplasm. Recognition of such biliary papillary neoplasm with respect to the pancreatic equivalent may lead to a better understanding and further studies of the intrahepatic biliary neoplasm.

Key words: Biliary papillary neoplasm, biliary papillomatosis, intrahepatic biliary tree, intrahepatic cholangiocarcinoma, peribiliary glands

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Introduction

A majority of intrahepatic cholangiocarcinoma (ICC) are known to develop in apparently normal livers (Nakanuma et al., 2000; Bernard and Nakanuma, 2001). As for the ICC arising in peripheral hepatic parenchyma, stem cells or bile ductules may be a precursor cell. ICC also arises in the intrahepatic large bile ducts (lining biliary epithelia and epithelial cells of the peribiliary glands) within the hepatic parenchyma and also at the hepatic hilus. While a great majority of ICC arising in the intrahepatic large bile ducts show luminal obliteration or stenosis with periductal infiltration of carcinoma cells and carcinomatous nodule formation, some of them show intraductal papillary growth and intraluminal spread with luminal dilatation (Colombari and Tsui, 1995; Kim et al., 1998). While the latter is reportedly common in chronic biliary diseases such as hepatolithiasis, they also occur alone. Biliary papillomatosis, intraductal growth type of ICC, mucin-producing ICC, intraductal mucosal-spreading mucin-producing peripheral cholangiocarcinoma, and intraductal growth type of peripheral cholangio-carcinoma, and biliary cystadenocarcinoma with continuous growth in the intrahepatic bile duct (Kim et al., 1989; Lim et al., 2000; Suh et al., 2000) seem to be included in this category. Several reports from East Asian countries, disclosed that these tumors have a better prognosis after surgical resection (Ohashi et al., 1995).

Our previous studies (Chen et al., 2001) disclosed that in hepatolithiasis, biliary papillary neoplastic lesions are not infrequently detectable in the intrahepatic bile duct and they are frequently associated with gastroenteric metaplasia and mucin hypersecretion. Interestingly, this type of papillary tumor resembles histologically, phenotypically and clinically intraductal

Abbreviations: CA 19-9, carbohydrate 19-9; CC, cholangiocarcinoma; CEA, carcinoembryonic antiben; CK, cytokeratin; ICC, intrahepatic cholangiocarcinoma; IPN-L, intraductal papillary neoplasm of the liver; IPMN-P, intraductal papillary mucinous neoplasm of the pancreas; MCN, mucinous cystic neoplasm of the pancreas; MUC, mucus core protein; PSC, primary sclerosing cholangitis

papillary mucinous neoplasm of pancreas (IPMN-P) (Nagai et al., 1995). In fact, Chen et al. (1998) reported that mucin-producing ICC comprises about 15% of ICC in Taiwan. Recently, we proposed to call such papillary neoplasm of the intrahepatic biliary tree seen in chronic biliary diseases collectively as "intraductal papillary neoplasia of the liver (IPN-L)" (Chen et al., 2001).

In this review, we would like to focus on the pathology of such biliary papillary neoplasms arising in the intrahepatic large bile ducts which includes biliary papillomatosis, intraductal growing cholangiocarcinoma in addition to IPN-L, and to propose that biliary papillary neoplasia seems to be a distinct and unique category of biliary neoplasm.

Anatomical and pathological basis for intrahepatic biliary neoplasm

Anatomy of intrahepatic biliary tree

The intrahepatic biliary tree is distal to the right and left hepatic duct, and is further divided into the intrahepatic large bile ducts, septal bile ducts, interlobular bile ducts, and bile ductules. The latter three are collectively called the intrahepatic small bile ducts (Nakanuma et al., 1997). According to Healey and Schroy's classification, the intrahepatic large bile duct is classified into the segmental duct (the first major branches of each hepatic duct: left medial and lateral, right anterior and posterior), area ducts (the first major branches of each segmental duct; anterior and inferior area ducts of each segmental duct), and their finer branches (Healey and Schroy, 1953). These intrahepatic large bile ducts are distributed at the hepatic hilus and also proximal to the middle of the hepatic parenchyma.

Histologically, the intrahepatic biliary tree is lined by a single layer of columnar or cuboidal epithelial cells. In addition, the intrahepatic large bile ducts are constantly accompanied by intrahepatic peribiliary glands which are regularly distributed on the both sides of these bile ducts and are composed of several lobules and their own conduits. Septal bile ducts are microscopically identifiable and are larger than the interlobular bile ducts. The intrahepatic large bile ducts and septal bile ducts accompany the dense fibrous wall (bile ductl wall). Interlobular bile ducts are less than 100 μm in their internal diameter, but lack periductal walls, and are accompanied by a portal vein and hepatic artery. Bile ductules are located adjacent to the periportal hepatocytes in the portal tracts and include the Canal of Hering.

Definition of biliary epithelial hyperplasia, metaplasia, and neoplasia (dysplasia and carcinoma)

The following pathological categories occur in chronic biliary disease and are related to the papillary proliferative lesion of the biliary epithelia of the intrahepatic large bile duct.

Hyperplasia

Hyperplasia of lining biliary epithelial cells of the large bile ducts is manifested as stratification, or micropapillary and/or papillary configuration. Peribiliary glands are also known to show hyperplasia of individual acinar cells and also of the glands themselves.

Biliary epithelial hyperplasia may precede dysplastic changes (hyperplasia-dysplasia-carcinoma sequence) which is seen during the neoplastic transformation of the biliary epithelium.

Metaplasia

The intrahepatic biliary tree shows several types of metaplasia.

Gastric (foveolar) and colonic metaplasia. Invaginated lining biliary epithelia into the bile duct wall transform to glandular structures resembling gastric foveola and pyloric glands (gastric metaplasia). This lesion expresses aberrantly the gastric type mucin MUC5AC and MUC6 (Sasaki et al., 1998). Colonic epithelial metaplasia resembling regenerating colonic epithelia and/or tubular adenoma of the colon also occur in hyperplastic and dysplastic biliary lining epithelia in chronic biliary disease and is positive for MUC2 and CK20 (Shimonishi et al., 2002). Goblet cell change is also frequently seen in the lining epithelial cells, while intestinal metaplasia characterized by Paneth's cells and/or brush border is occasionally encountered in pathological peribiliary glands, but rarely in the biliary lining epithelia (Kurumaya et al., 1989).

Other metaplasia: Neuroendocrine cells which are physiologically located in the peribiliary glands, increase in their number in proliferated peribiliary glands in hepatolithiasis (neuroendocrine metaplasia). They are usually positive by Grimelius staining and by immunostaining for chromogranin A. In addition, several types of hormones, particularly somatostatin and gastrin, become increasingly detectable in these conditions (Kurumaya et al., 1989). Squamous metaplasia is rarely encountered in the large intrahepatic bile duct in primary sclerosing cholangitis (PSC) or other long-standing biliary diseases or in the biliary cysts.

Biliary Epithelial Neoplasia

This lesion may be divided into two categories: biliary epithelial dysplasia and in situ and invasive carcinoma. The main differential histological features for these lesions are shown in Table 1.

Biliary epithelial dysplasia: This is defined as foci of biliary epithelial cells showing multilayering, piled up nuclei, an increased nucleo-cytoplasmic ratio, a partial loss of nuclear polarity, cellular and nuclear

polymorphism and polarity, and nuclear hyperchromasia (Nakanuma et al., 2000). However, these atypical features are mild and inadequate for making a diagnosis of carcinoma. This dysplastic lesion shows an abrupt transition of abnormal cytological and structural alterations against the surrounding non-dysplastic biliary epithelium. These changes are dividable into low-grade and high-grade dysplasia due to cellular and nuclear alterations. This change is seen in the lining epithelia and also in the proliferated peribiliary glands. Cytologically, the dysplastic cells could be a neoplasm (intraepithelial neoplasm). Biliary epithelial dysplasia is found in the biliary epithelia showing papillary growth or micropapillary proliferation with fibrovascular cores in the ductal lumen, and also in the non-papillary biliary epithelium. Metaplastic changes are not infrequently superimposed on this dysplastic lesion. Dysplasia in an inflammatory melieu may be difficult to distinguish from reactive or regenerative atypia.

In situ carcinoma, and microinvasive and invasive ICC

ICCs arising from the intrahepatic large bile duct and hilar bile ducts are categorizable into *in situ* carcinoma, and microinvasive and invasive carcinoma. *In situ* carcinoma is an intraepithelial malignancy with or without peribiliary glandular involvement. Microinvasive ICC is defined as focal and minimal invasion of carcinoma in the ductal wall and periductal tissue which is recognizable microscopically. Invasion of carcinoma could be recognizable grossly and microscopically in invasive ICC. *In situ* and microinvasive carcinoma and biliary dysplasia are frequently recognizable in the presence of chronic biliary diseases. The morphological distinction between high grade dysplasia and *in situ* carcinoma are determined by the combination of cellular and structural atypia of neoplastic biliary epithelia (Table 1). Carcinoma cells show increased mitosis and occasional abnormal mitosis and also other characteristics of malignant tumors.

Definition and subclassification of IPN-L

IPN-L is defined as an intraductal papillary or villous growth of neoplastic biliary epithelia with fine fibrovascular cores in the bile duct lumen of the intrahepatic biliary tree in hepatolithiasis (Chen et al., 2001). Branching papillary fronds are lined by columnar to cuboidal epithelial cells with basal nuclei located (Fig. 1). The lumen of the affected ducts is dilated due to stones and biliary sludges as well as mucin. Lining epithelia of IPN-L is either of biliary epithelial type or shows variable gastroenteric metaplasia. The IPN-L is divided into 4 groups according to dysplastic and carcinomatous changes: IPN-L lined by low grade dysplasia; that by high grade dysplasia, that by carcinoma in situ and/or microinvasive adenocarcinoma, and that by carcinoma with variable invasion. Low-grade and high-grade dysplasia are also variably present in the latter two categories. IPN-L is included in biliary papillary neoplasia in this review.

Biliary papillary neoplasia of the liver

There have been several studies on biliary papillary neoplasia (Kim et al., 1989, 1998; Amaya et al., 2001), though the etiopathogenesis of this neoplasia has not been well characterized, so far. These biliary papillary neoplasms may arise in the presence of chronic hepatobiliary diseases, whereas some cases also develop alone. Mucin hypersecretion is a frequent manifestation of biliary papillary neoplasia, and secreted mucinous substances in addition to soft fragile tumor projections or masses fill the affected dilated bile duct lumen.

Intraductal-growing cholangiocarcinoma and biliary papilloma and papillomatosis in the absence of chronic biliary diseases

Intraductal growing cholangiocarcinoma

CC could be grossly categorized as multinodular and massive lesion or spreading lesion along the intrahepatic

Table 1. Histologic criteria of low grade dysplasia, high grade dysplasia and in situ adenocarcinoma seen in intraductal papillary neoplasm of the liver in hepatolithiasis*

	LOW GRADE DYSPLASIA	HIGH GRADE DYSPLASIA	IN SITU ADENOCARCINOMA
Increased N/C ratio*	slight	moderate	marked
Loss of nuclear polarity	slight	moderate	marked
Nuclear hyperchromsia	sight	moderate	marked
Nuclear pleomorphism	slight	moderate	marked
Abnormal mitosis	absent	few	present
Prominent nucleoli	inconspicuous	conspicuous	conspicuous
Cribriform structure	absent	present	present
Multilayering	present	present	present
Piled-up nuclei	mild	present	present
Abrupt transition to the adjacent biliary epithelia	present	present	present
Glandular involvement	absent to mild	mild to moderate	mild to marked

N/C ratio: nucleo-cytoplasmic ratio; *: modified from Chen et al. (2001).

biliary tree. Intraductal-growing cholangiocarcinoma is also identifiable particularly at surgically resectable stages. Previously reported terms such as mucin-producing ICC, intraductal mucosal-spreading mucin-producing peripheral cholangiocarcinoma, intraductal growth type of peripheral cholangiocarcinoma, and intraductal variant of peripheral cholangiocarcinoma, are related or identical to the intraductal growing cholangiocarcinoma. Although there have been a number of clinical and genetic studies on this type of ICC, the histogenesis and progression of this type remains speculative.

In the intraductal-growing type, the affected bile ducts show marked dilatation, and the tumors are grossly confined within the dilated part of the bile duct, with no or mild tumorous extension beyond the bile duct walls. This type is the least common among ICCs and shows a rather better prognosis after complete surgical resection. Recently, this type has received attention in Asian countries. For example, Suh et al. (2000) and Ohashi et al. (1995) reported that 16 cases among 122 surgically-resected ICCs (14.3%) in Korea and 6 cases among 72 surgically resectable cases of ICC in Japan were of this type, respectively. While the former showed a male predominance (Suh et al., 2000), the difference of gender could be due to ethnic background, environment, and diet.

Biliary papillomatosis

Biliary papillomatosis is a rare papillary or villous tumor of variable distribution and extent in the intrahepatic and/or extrahepatic biliary tree which shows cytological and histological atypia, though not enough for a diagnosis of malignancy (Okulski et al., 1979; Gunven et al., 2000; Loo et al., 2001). Papillary, fragile tumors are seen on the inner surface of the dilated biliary tree either multiply or diffusely. In some cases, the papillary tumor is confined to one segment of the intrahepatic biliary tree (Terada et al., 1991). While they are of neoplastic characters, histopathological features and biological behaviors of this disease remain non-malignant. Patients of biliary papillomatosis are middle-aged or elderly, and males and females are equally affected. The papillary epithelia of this lesion are histologically dividable into biliary or metaplastic types (Amaya et al., 2001). The gastric metaplastic type is common in the latter, though intestinal-type papillomatosis, extensively showing Paneth's cell metaplasia is occasionally experienced (Bae et al., 2002). The biliary type shows tall columnar epithelia with basal nuclei and minimal pleomorphism, occsaionally associated with malignant transformation. While this tumor appears to follow a much less aggressive clinical course and the carcinomatous infiltration into the surrounding liver and also extrahepatic metastases are rare, this tumor has a great potential for malignant transformation. It can grow intraluminally and mulitply and spread along and within the biliary (Neumann et al., 1976), and some cases progress to invasive, mucin-producing papillary carcinoma, especially at the terminal stages (Kim et al., 2000).

Biliary papillary lesions (hyperplasia, dysplasia, and in situ and microinvasive carcinoma) in chronic hepatobiliary diseases

In chronic biliary diseases, intraductal papillary proliferation of neoplastic biliary-lining epithelium with a fine fibrovascular core is occasionally encountered . Such lesions are tentatively termed "intraductal papillary

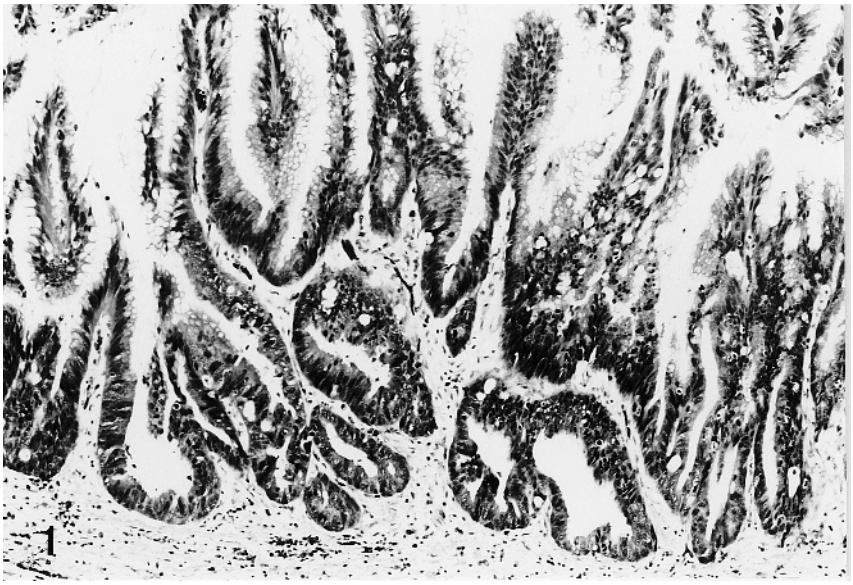

Fig. 1. Biliary epithelia show papillary configureation with a fine fibrovascular core. Histological diagnosis is high grade dysplasia. HE staining, hepatolithiasis. x 120 (from Chen et al., 2001).

neoplasm of the liver (IPN-L)" in this review. Papillary growth of IPN-L is usually multifocal, and shows a variable but usually extensive intraluminal spread. They resemble grossly and histologically the above-mentioned biliary papillomatosis, and also intraductal-growing cholangiocarcinoma with no or variable invasion (Kim et al., 1989; Ohta et al., 1991). In addition, they also show low-grade and high-grade dysplasia, usually with microscopic and occasionally macroscopic papillary configurations. In this sense, biliary papillary neoplasm in chronic biliary disease (IPN-L) composes a continuous histological spectrum of neoplastic biliary neoplasm from dysplasia to carcinoma with papillary configuration (Chen et al., 2001).

IPN-L in hepatolithiasis

PNL-L in Taiwan shows an obvious female predominance; middle- to old-age distribution. Interestingly, hepatolithiasis patients with INP-L are older than those without INP-L and the proportion of women is higher for hepatolithiasis with IPN-L than without. In Japan, such female predominance is not evident, and the incidence of IPN-L in hepatolithiasis is low (12 out of 135 hepatolithiasis cases) (Chen et al., 2001). Ohta et al. (1991) reported that 4 out of 32 hepatolithiasis cases are associated with intraductal growing ICC. Almost all stones in hepatolithiasis with IPN-L are of calcium bilirubinate, and cholesterol stones are exceptional (Nakanuma et al., 1985).

Gross and microscopic features: IPN-L is preferentially found in the stone-containing intrahepatic large bile ducts and in the adjacent non-dilated bile ducts. Ohta et al. (1991) reported that IPN-L is preferentially found in the peripheral sites of stones. INP-L is frequently located in the left lobe and to a lesser frequency in the right lobe. The cut surface of the resected liver specimens showed marked dilatation of the stone-containing intrahepatic bile ducts (Fig. 2). Mucobilia were grossly evident in about a half of the cases with in situ or invasive carcinoma (Fig. 3). The intrahepatic large bile duct or its branch(es) were variably filled with sticky mucin. Such gross findings are useful in the diagnosis of IPN-L, particularly at the time of surgery. In IPN-L, mucin overproduction is more frequent in in situ or microinvasive and invasive carcinoma than in low-grade or high-grade dysplasia (Table 2), and mucinous carcinoma is frequent in ICC arising in hepatolithiasis in Taiwan. By contrast, mucobilia and mucinous carcinoma were rather infrequent or rare in Japanese IPN-L cases.

Microscopically, the non-neoplastic bile ducts shows

Table 2. Mucin production in papillary biliary epithelia of intraductal papillary neoplasm of the liver (62 cases) in Taiwan.

	LOW GRADE DYSPLASIA (23 cases)	HIGH GRADE DYSPLASIA (11 cases)	IN SITU OR MICROINVASIVE CARCINOMA (13 cases)	INVASIVE CARCINOMA (15 cases)
Mucin over production	5 (21.7%)	6 (54.5%)	11(84.6%)	12 (80%)
Mucobilia	0	0	5 (38.5%)	9 (60%)
Mucus Extravasation*	0	0	2 (15%)	10 (66.7%)

%: percent of positive cases; *, $p<0.01$

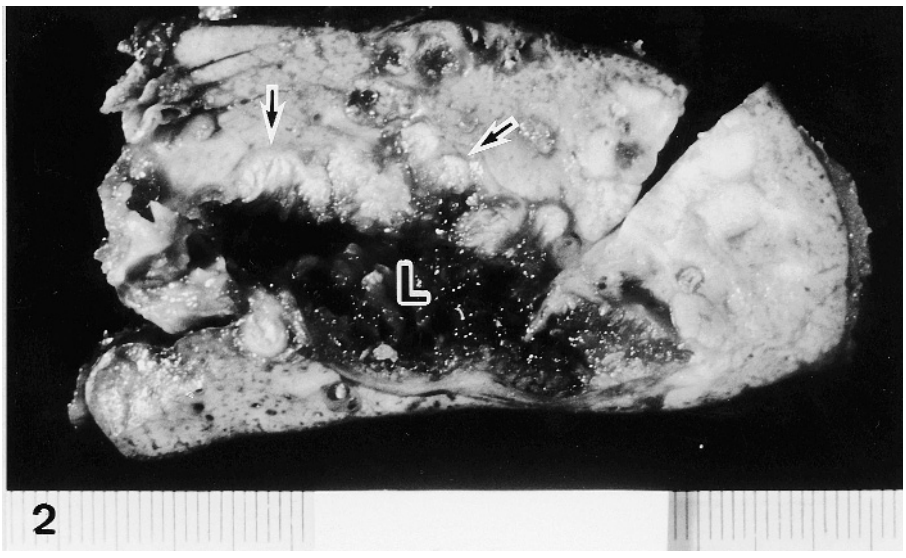

Fig. 2. Gross features of biliary papillary neoplasia with mucus hypersecretion in hepatolithiasis. Histologically, well differentiated papillary adenocarcinoma with minimal invasion. Arrows denote papillary projection of neoplastic biliary epithelia. L: bile duct lumen (from Chen et al., 2001).

moderate to marked chronic proliferative cholangitis, and peripheral bile duct obliteration (Nakanuma et al., 1989). Fine papillary tumor tissues were found in the dilated stone-containing large bile ducts (Figure 1). The *in situ* carcinoma and dysplasia, particularly the high-grade type, shows intraductal spread along the luminal surface. In addition, the involvement of the peribiliary glands and their conduits by neoplastic biliary epithelial cells is also common. In IPN-L with *in situ* or invasive carcinoma, there is variable involvement of the intrahepatic small bile ducts, reflecting intraductal spread. These findings suggest that while surgical resection of IPN-L, particularly for *in situ* and invasive carcinoma, is essential in the treatment of this type of ICC, recurrence from the peripheral bile ducts containing foci of intraductal spread may occur. It is therefore important for surgeons to remove the foci of intraductal spread as thoroughly as possible. Mucinous hypersecretion associated with mucobilia is also one of the frequent features.

At advanced stages or invasive areas of 15 cases of IPN-L, 4 showed mucinous carcinoma and 6 showed elements of mucinous carcinoma in addition to moderately- and poorly-differentiated adenocarcinoma. The remaining cases showed moderately-differentiated adenocarcinoma or adenosquamous carcinoma (Table 3).

Table 3. Histology of invasive areas of intrahepatic cholangiocarcinoma related to intraductal papillary neoplasm of the liver in hepatolithiasis in Taiwan.

CASE	HISTOLOGY OF INVASIVE AREAS OF INTRAHEPATIC CHOLANGIOCARCINOMA
1	Mucinous ca. predominant
2	Mucinous ca. predominant
3	Mucinous ca. predominant
4	Mucinous ca. predominant
5	Mucinous ca. < moderately differentiated adenoca.
6	Mucinous ca. < moderately differentiated adenoca.
7	Mucinous ca. < moderately differentiated adenoca.
8	Mucinous ca. < moderately differentiated adenoca.
9	Mucinous ca. < moderately differentiated adenoca.
10	Mucinous ca. < poorly differentiated and papillary adenoca..
11	Poorly + moderately differentiated adenoca.
12	Moderately differentiated adenoca.
13	Moderately differentiated adenoca.
14	Moderately differentiated adenoca.
15	Adenosquamous cell carcinoma

adenoca: adenocarcinoma

Gastroenteric metaplasia. Biliary epithelial cells in IPN-L frequently show gastroenteric metaplasia such as colon-like, foveolar and goblet cell metaplasia. In accordance with this type of metaplasia, aberrant expression of CK20, MUC2, MUC5AC and/or MUC6, a phenotypic marker of gastroenteric and intestinal metaplasia (Chen et al., 2001; Shimonishi et al, 2002), are frequently observed in IPN-L arisen in the intrahepatic large bile ducts of hepatolithiasis. This is also the case in the biliary papillomatosis. Interestingly, IPN-L cases showed negative or focal expression for CK7, a biliary epithelial marker, while such IPN-L shows moderate/extensive expression of CK20, MUC2 and/or MUC5AC. Neo-expression or increased expression of CK20 and MUC2 was significantly correlated with the progression of IPN-L. These gastroenteric metaplasia are significantly associated with mucin overproduction and are manifested by mucobilia as well as mucus extravasation.

Neutral, sialo- and sulfomucin. There is a characteristic pattern of the mucin profile associated with IPN-L

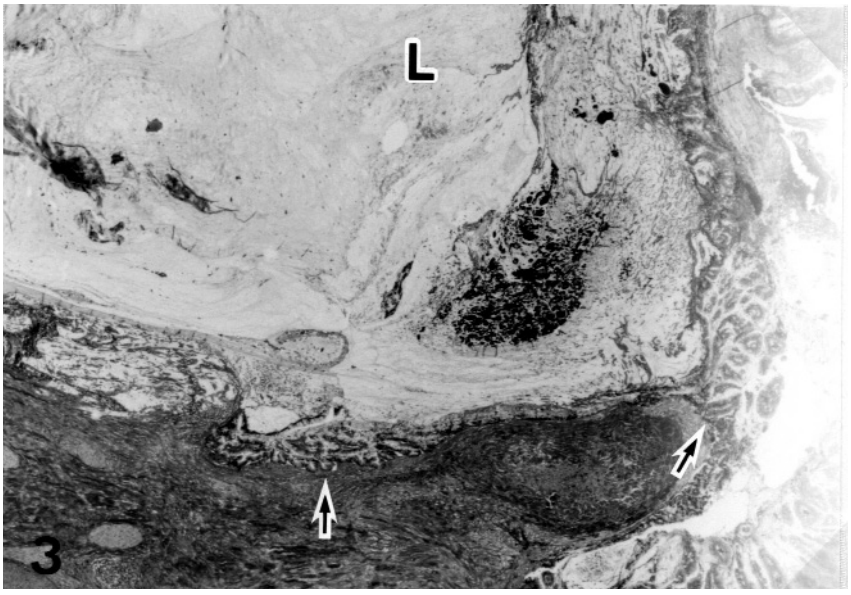

Fig. 3. Intraductal growing cholangiocarcinoma (arrows) with microinvasion and mucin hypersecretion. Bile duct lumen (L) is expanded by much mucin. HE staining, hepatolithiasis. x 40 (from Chen et al., 2001).

progression. That is, non-neoplastic intrahepatic large bile ducts are strongly positive for di-PAS, and more predominantly for HID (sulfomucin) than AB alone (sialomucin). While dysplastic and carcinomatous biliary epithelial cells are strongly positive for di-PAS in IPN-L, the reduction of sulfomucin expression and the reciprocal increase of sialomucin expression is closely correlated with the histological progression of IPN-L. Increased sialomucin expression is well known to correlate with the degree of dysplasia in colorectal carcinoma (Hanish et al.1992).

Oncofetal markers and cell kinetics. Carbohydrate antigen (CA) 19-9 is observed diffusely in the cytoplasm of dysplastic lesions and carcinomas of IPN-L, and carcinoembryonic antigen (CEA) is restricted to the luminal surface and/or the supra-nuclear region of the cytoplasm in high-grade dysplasia, and is variably expressed in carcinoma cells in IPN-L (Shimonishi et al. 2002).

P53 and oncogenes. It is found that p53 protein expression was significantly correlated with the progression of IPN-L (Shimonishi et al., 2002), suggesting that p53 dysregulation might have been a middle to late genetic change in the development and progression of ICC during IPN-L. However, the incidence of p53 protein expression in IPN-Ls (30%) was lower than the incidence seen in non-papillary ICCs (65%). A point mutation at codon 12 of the K-ras oncogene was found in the papillary lesion in a case of biliary papillomatosis associated with congenital choledochal cyst and hepatolithiasis (Ohta et al., 1993). Biliary irritation associated with hepatolithiasis may be related to IPNL-L with point mutation at codon 12 of K-ras gene. Dysregulation of other oncogenes and anti-oncogenes have not been examined in detail with an emphasis on IPN-L, so far.

Carbohydrate antigens. There are several reports on the expression of carbohydrate antigens (T, Tn and STn) in normal bile duct and its malignant derivatives (Amaya et al., 2001). Expression of MUC1, Tn antigen and sialosyl Tn antigen was frequent and marked in biliary papillomatosis alone and with carcinoma. In addition, a marked expression of MUC1 and Tn antigen was rather frequent in biliary papillomatosis with carcinoma compared to biliary papillomatosis alone. Focal expression of T-antigen was frequent in papillary intraductal cholangiocarcinoma.

Biliary papillary lesions in other chronic biliary diseases

ICC is known to occur in liver fluke infestations, PSC, and congenital biliary anomalies affecting the intrahepatic biliary tree. Such hepatobiliary diseases could also lead to the formation of IPN-L.

Liver Fluke. In liver fluke infestation, such as *Clonorchis sinesi*s and *Opisthorchis veverrini*, the intrahepatic bile ducts first show desquamation of the biliary epithelial with subsequent development of adenomatous hyperplasia and periductal fibrosis in addition to inflammation and goblet cell metaplasia (Kim et al.1989). Neoplastic transformation from such adenomatous change in bile ducts to ICC through dysplastic changes is also suspected in *Opisthorchiasis*. The intraductal-growing cholangiocarcinoma reported by Suh et al. (2000) account for one-third of patients with a history of *Clonorchis sinensis* infestation, though the exact cause and result relationship is speculative.

PSC. Ludwig et al. (1992) reported multiple papillary mucosal lesions in the right and left hepatic ducts in patients with PSC. The papillary lesions with low-grade and high-grade dysplasia and one focus of microinvasion seem to be similar to IPN-L. Interestingly, some peribiliary glands were also dysplastic in their cases. Detailed macroscopic and microscopic review of 23 livers from their patients with the longest history of PSC (range, 5-24 years) failed to reveal any additional cases with dysplasia. The prevalence of dysplasia and carcinoma of large bile ducts may be less than the 7%-9% reported in the literature for malignancies associated with PSC.

Others. Biliary papillary neoplasm arising in cholangiectatic anomalous bile ducts in Caroli's disease and other diseases is also known (Gallagher et al., 1972; Ohta et al., 1993; Yamato et al., 1998).

Histological progression from chronic proliferative cholangitis to *in situ* cholangiocarcinoma in chronic hepatobiliary diseases.

Bile stagnation, altered bile and mucin composition, and bacterial infection of the biliary tree may be responsible for lithogenesis, and also for chronic proliferative cholangitis in hepatolithiasis. The latter reflects an active and long-standing inflammation of the stone-containing bile ducts, showing a hyperplasia of lining epithelia and the proliferation of peribiliary mucus glands (adenomatous hyperplasia) and periductal inflammation and fibrosis (Kim et al., 1989). This may give rise to the development of biliary papillary lesions via mucosal epithelial drop-out and reparative hyperplasia. Lining epithelium of the intrahepatic large bile duct, when persistently exposed to biochemically altered bile and bacteria, may undergo a carcinomatous transformation through a stage of biliary dysplasia. A continuous histological spectrum of biliary papillary hyperplasia and dysplasia with variable metaplasia and then *in situ* and invasive cholangiocarcinoma may evolve. This sequence is schematically shown in Figure 4. Various amounts of mucinous carcinoma are frequently present in advanced stages of IPN-L (Table 3). The development and progression of biliary papillomatosis may also accompany reduced biliary phenotype and increased gastro-intestinal phenotype.

Accumulation of genetic alterations including p53 dysregulation eventually lead to *in situ* and invasive carcinomas (progression of neoplasm), suggesting the multistep carcinogenesis of IPN-L. Gastroenteric metaplasia in IPN-L may relate to frequent occurrence of mucinous elements, compared to non-papillary ICC.

Related diseases and differential diagnosis

There are several hepatobiliary lesions or diseases resembling or related to biliary papillary neoplasm. Interestingly, several intraductal or intracystic papillary diseases in the pancreas resemble or are related to these biliary papillary neoplasm, suggesting common pathophysiological and developmental processes in the biliary tree and pancreatic duct (Sirica and Longnecker, 1997).

Biliary mucinous cystadenoma and cystadenocarcinoma

Biliary mucinous cystadenoma and cystadenocarcinoma are composed of multiloculated cyst(s) with intracystic multifocal papillary epithelial lesions. The former occurs in women, is associated with mesenchymal stroma, and has a good prognosis after total surgical resection of the tumor. In contrast, the latter occurs equally in men as well as women, and some are associated with mesenchymal stroma and others not (Wheeler and Edmondson, 1985). The lining epithelia of the cysts are columnar cuboidal epithelium with mucin-positive clear cytoplasm and show variable cellular and structural atypia. Recently, two cases of oncocytic biliary cystadenocarcinoma without mesenchymal stroma are reported, and they are composed of carcinoma cells with an acidophilic granular cytoplasm containing many mitochondria, resembling oncocytes (Wolf et al., 1992; Sudo et al., 2001). Grossly, these mucinous or oncocytic type tumors exhibited mucin-filled cysts containing papillary projections. The invasive portion was also a mucinous carcinoma.

The oncocytic type could be regarded as a variant of mucinous biliary cystadenocarcinoma. The histogenesis and clinicopathological features of mucinous biliary cystadenocarcinoma with and without mesenchymal stroma, may differ (Devaney et al., 1994). The latter tends to show a poor prognosis compared to the former. Some of mucinous biliary cystadenocarcinoma without mesenchymal stroma, including the oncocytic variant, reportedly show communication with the intrahepatic biliary tree by cholangiography. The papillary carcinoma or high-grade dysplasia similar or identical to the lining neoplastic epithelia of the cysts sometimes grow in the neighboring intrahepatic bile ductal lumen, suggesting the direct continuation of neoplastic cells between both regions. It seems plausible that some of the biliary mucinous cystadenocarcinoma without mesenchymal stroma are an extended form or strangulated form of biliary papillary neoplasm with secondary neoplastic cyst formation filled by mucin.

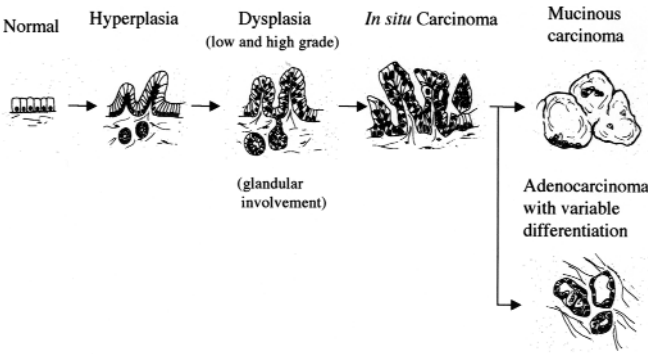

Fig. 4. Histological sequence of biliary papillary neoplasia (intraductal papillary neoplasm) of the liver in hepatolithiasis.

Interestingly, similar scenario is also proposed in mucinous cystic neoplasm (MCN) and intraductal papillary mucinous neoplasm (IPMN-P) in the pancreas. The former is associated with mesenchymal stroma, while the latter is not. A vast majority of cases of IPMN-P, which is characterized by predominantly intraductal growth of papillary tumor with mucus hypersecretion, are known to develop secondary cystic changes or saccular dilatation of involved ducts resembling MCN. Characteristically, much mucin produced by the neoplastic cells is usually present in the dilated pancreatic ducts and their branches (mucinous ductal ectasia) (Nagai et al., 1995). Both frequently show gastroenteric metaplasia, and intraductal papillary growth and spread. Both frequently show multicentric occurrence and development. Interestingly, two thirds of IPN-L with invasive carcinoma contain elements of mucinous carcinoma and show mucinous carcinoma in some cases (Table 3). In addition, the biliary papillary tumor is histologically classified into dysplasia, *in situ* carcinoma or invasive carcinoma, and IPMN-P is also classified into either hyperplasia, adenoma, or adenocarcinoma. The main similarities between biliary mucinous cystadenoma and cystadenocarcinoma with mesenchymal stroma and MCN, and between biliary papillary neoplasm and IPMN-P, are shown in Tables 4 and 5 (Sudo et al., 2001).

Biliary papillary neoplasia including IPN-L in chronic biliary diseases share the pathological, clinical and radiological features of IPMN-P (Kim et al., 2000). The relatively good prognosis of biliary papillary neoplasm after complete surgical resection is also similar and comparable to that of IPMN-P. In fact, a case of biliary papillary tumor with IPMN-P is actually reported (Joo et al., 2000). Taken together, biliary papillary neoplasia including IPN-L could be regarded as a special form of biliary neoplasm and appears to be a hepatobiliary equivalent of IPMN-P. However, some cases of biliary papillary neoplasm were not associated with mucin hypersecretion and mucobilia (Kim et al., 1998; Chen et al., 2001).

Oncocytic biliary cystadenocarcinoma resembles intraductal oncocytic papillary neoplasm of the pancreas

in development and progression (Adsay et al.,1991). The latter shows marked cystic dilatation of the pancreatic duct and resembles IPMN-P in its development and progression. Similar scenario is also the case in the oncoctic biliary cystadenocarcinoma (Sudo et al., 2001). This is also interesting because a substantial proportion of the invasive carcinomas arising in IPMN-P and biliary papillary neoplasm progress to mucinous carcinoma (Chen et al., 2001).

Hepatic peribiliary cysts

The cysts located around the intrahepatic large bile ducts are thought to arise from cystic dilatation of the peribiliary glands (Nakanuma et al., 1984). They range in size from a microscopic level to a few cm, occasionally up to 3 cm. These cysts are shown not to be connected with the lumen of the intrahepatic large bile ducts (Itai et al., 1994; Kudo et al., 2001). While these lesions develop preferentially in patients with chronic hepatobiliary diseases with portal hypertensive diseases, they are also often seen in the livers of adult polycystic liver and kidney disease patients and to a lesser degree in those with solitary non-parasitic liver cysts (Kida et al., 1992). To a varied degree, these cysts are associated with inflammatory and hyperplastic changes of their epithelial lining, and the peribiliary glands themselves are increased in their number and distribution (Terada and Nakanuma, 1990). The peribiliary glands at these cystic areas expressed c-MET protein, the HGF receptor which may be related, at least in part, to the cystic dilatation of the peribiliary glands (Fujioka et al., 1997). Lack of familiarity with this pathology could lead to an erroneous diagnosis of well-differentiated hilar cholangiocarcinoma or biliary cystadenoma or cystadenocarcinoma.

Metastatic colorectal carcinoma

Colorectal carcinoma metastasis is frequent in the liver (Maeda et al., 1996; Rullier et al., 2000). Usually, metastatic colorectal carcinoma as a whole shows nodules in the hepatic parenchyma. However, a few cases of colorectal carcinoma show metastatic lesions with intraductal growth of the bile ducts with obstructive jaundice. This typically shows papillary growth in the dilated intrahepatic bile duct, resembling biliary papillary neoplasia (Maeda et al., 1996). Metastatic colorectal adenocarcinoma is positive for CK20 and MUC2 but negative for CK7, though a majority of ICC are positive for CK7 but usually negative or only focally positive for CK20. This character used to be applied for the distinction of such metastatic carcinoma from primary ICC. However, IPN-L, particularly that with colonic metaplasia, shows similar cytokeratin and MUC profiles as those seen in metastatic colorectal carcinoma (Shimonishi et al., 2002). So, a combination of CK 20 and CK 7 may be limited for the differential diagnosis of IPN-L from papillary metastatic colorectal carcinoma.

Table 4. Comparison of biliary mucinous cystadenoma and mucinous cystic neoplasm of the pancreas*.

	BILIARY MUCINOUS CYSTADENOMA AND CYSTADENOCARCINOMA WITH MESENCHYMAL STROMA	MUCINOUS CYSTIC NEOPLASM OF THE PANCREAS WITH MESENCHYMAL STROMA
Multicystic lesions	always	always
Mucin hypersecretion	always	always
Ductal involvement and dilatation	rare or absent	rare or absent
Mesenchymal stromal wall	always	always
Prognosis after surgical resection	good	good
Communication with the main duct	absent	absent
Sex and gender	frequent in middle -aged women	frequent in middle -aged women

*: modified from Sudo et al (2001).

Table 5. Comparison of intraductal mucin-producing papillary cholangiocarcinoma and intraductal papillary mucinous neoplasm of the pancreas*

	BILIARY PAPILLARY NEOPLASM	INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM OF THE PANCREAS
Ductal involvement and dilatation	frequent	frequent
Multicystic lesions (secondary) filled with mucin	frequent	frequent
Mucin hypersecretion	frequent	frequent
Communication with main duct	identifiable sometimes	identifiable sometimes
Advanced form	frequently colloid carcinoma	frequently colloid carcinoma
Oncocytic variant	occasional	occasional
Gender	male as well as female	male as well as female

*: modified from Sudo et al (2001).

Perspectives

Biliary papillary neoplasia of the intrahepatic biliary tree develops alone or evolves in the presence of chronic biliary diseases such as hepatolithiasis or liver flukes infestation. Interestingly, this neoplasm resembles intraductal papillary mucinous neoplasm of the pancreas (IPMN-P), morphologically, phenotypically and clinically. The comparative studies of biliary and pancreatic papillary neoplasm are mandatory of both tumors with respect to etiopathogenesis and multi-step carcinogenesis. Genetic and phenotypic studies of IPMN-P and early detection of genetic products rather specific to IPMN-P are in progress. Frequent gastroenteric metaplasia of these neoplasia, particularly colonic metaplasia, may be responsible for mucinous carcinoma components. Such biliary papillary neoplasm is reportedly not common, though its incidence is probably underestimated. More attention of this disease entity, particularly at the time of biliary imagings and surgery, may lead to more discovery of this disease. Hopefully, this review opens this interesting field of carcinogenesis or tumorigenesis of the biliary tree. Further studies on biliary papillary neoplasia with respect to IPMN-P may explore new fields of carcinogenesis of the biliary tree.

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