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Review

Proposal of a new disease concept "biliary diseases with pancreatic counterparts". Anatomical and pathological bases

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Summary. The biliary tract and pancreas are located closely anatomically, and both develop from the endoderm foregut almost at the same time. Interestingly, the lining epithelia of the bile duct and main pancreatic duct show similar morphologies and phenotypes, and both are accompanied by periductal glands. Furthermore, the exocrine pancreatic acini are remnantly found in the peribiliary glands. Based on these findings, it seems plausible that the biliary tract has features of pancreatic elements in addition to the duct system, which is specialized for the drainage of bile secreted by hepatic parenchyma, particularly, hepatocytes. Interestingly, some pancreatic and biliary diseases show similar pathological features and even biological behaviors. For example, extrahepatic cholangiocarcinoma and ductal adenocarcinoma of the pancreas share many clinicopathological features. Both of them are hypothesized to arise from similar preneoplastic and early neoplastic intraepithelial lesions. Intraductal papillary tumors, with frequent mucin hyperproduction, develop in the pancreas (intraductal papillary mucinous neoplasm) and also in the biliary tract (intraductal papillary neoplasm of the bile duct). IgG4-related disease affects the biliary tract (IgG4-related sclerosing cholangitis) and the pancreas (autoimmune pancreatitis) in the same patients, with both showing similar morphologies. Herein, we propose that these non-neoplastic and neoplastic biliary diseases showing similarities to corresponding pancreatic diseases could be included in a new disease concept "biliary diseases with pancreatic counterparts". Based on this new concept, information obtained in biliary tract diseases could be applied to the analysis of pancreatic disease and vice versa, and also novel therapeutical strategies and molecular and genetic studies on pancreatic and biliary diseases may be developed with a unified approach.

Key words: Biliary tract, Pancreas, Duct adenocarcinoma, Intraepithelial neoplasm, Periductal glands

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Introduction

As experienced routinely, some pancreatic and biliary tract diseases show similar pathological changes and biological behaviors (Nakanuma et al., 2010a; Zen et al., 2006a,b). For example, autoimmune pancreatitis (AIP) and IgG4-related sclerosing cholangitis (IgG4-SC) show similar pathological features, and furthermore both frequently overlap in the same patients (Nakanuma and Zen, 2007; Zen et al., 2004). In addition, some neoplastic diseases such as intraductal papillary tumors, with frequent mucin hyperproduction, develop in the pancreas (intraductal papillary mucinous neoplasm, IPMN) as well as the biliary tract (intraductal papillary neoplasm of the bile duct, IPNB) (Chen et al., 2001; Nakanuma et al., 2010b; Zen et al., 2006a). These findings suggest that some pathological conditions may cause similar pathological features in the biliary tract and pancreas, though the reasons for these similarities remain to be clarified.

Anatomically, the biliary tract and pancreas are adjacent to each other, and the lining epithelia of the biliary tract and main pancreatic duct also show similar histologies (Gandou et al., 2013). Furthermore, there are glandular elements around the biliary tree (peribiliary glands) and pancreatic ducts (pancreatic duct glands) (Strobel et al., 2010; Terada et al., 1987, 1990; Yamaguchi et al., 2011, 2012). The former are physiologically located around the extrahepatic and intrahepatic large bile ducts (Terada et al., 1987, 1990). These glands are found within the ductal wall (intramural glands) and also in the periductal connective tissue (extramural glands). The latter are branched tubuloalveolar seromucous glands. Interestingly, pancreatic exocrine acini are infrequently intermixed with seromucous acini in the peribiliary glands (Fig. 1), and pancreatic exocrine enzymes such as trypsin and lipase are immunohistochemically detected in the exocrine pancreatic acini and seromucous acini of these peribiliary glands (Terada et al., 1987, 1993). These peribiliary glands drain into the lumen of the biliary tract via their own conduits (Ishida et al., 1989); thus, the biliary tract plays a role in the drainage duct of secretions from peribiliary glands in addition to that of bile secreted from hepatic parenchyma.

Furthermore, embryologically, the ventral pancreas and biliary system arise from the posterior ventral foregut at almost the same time (Eberhard et al., 2008). The transcription factors hairy and enhancer of split-1 (HES1) and pancreatic duodenal homeobox factor-1 (PDX1) are reportedly involved in the development of the ventral pancreas and extrahepatic biliary tract (Terada et al., 1987, 1990; Sumazaki et al., 2004). The anatomical and embryological relationship of the biliary tract and pancreas may be one of the reasons for the development of diseases affecting the biliary tract and pancreas that present similar pathological features (Nakanuma, 2010). Therefore, it seems plausible that some pancreatic diseases may also affect the pancreatic elements of the biliary tract (Fig. 2A-C).

In this review, we first describe several neoplastic and non-neoplastic biliary and pancreatic diseases with similar pathological and even clinical features. We then propose a new disease concept of "biliary diseases with pancreatic counterparts" (Table 1), and attempt to explain why these diseases resemble each other based on anatomical, developmental, and pathological aspects.

Neoplastic diseases of the biliary tract and pancreas showing similar pathological features and/or biological behaviors

Extrahepatic cholangiocarcinoma and ductal adenocarcinoma of the pancreas

Cholangiocarcinoma (CC) arising in the distal bile ducts and perihilar bile ducts (extrahepatic cholangiocarcinoma, ECC) and ductal adenocarcinoma of the pancreas (PDAC), the most frequent and significant malignant neoplasms of the biliary tract and pancreas, show similar pathological features and biological behaviors (Hruban et al., 2010; Gandou et al., 2013). ECC and PDAC commonly show an infiltrative growth pattern with nodular-sclerosing growth features without capsule formation, and histologically, they are typically well to moderately differentiated tubular and/or micropapillary adenocarcinomas with abundant desmoplastic reactions (Fig. 3A,B). They frequently show lymphatic, vascular and also perineural invasions. Clinically, both affect elderly adults, and are intractable malignant tumors that are commonly resistant to surgical and chemotherapeutic approaches. Both are frequently detected at an advanced stage, and show a poor prognosis in spite of therapies. ECC and PDAC patients also show similar post-operative survival courses. Interestingly, some patients with ECC and also PDAC are known to respond well to TS-1 and Gemstabin chemotherapy (Heinemann et al., 2013; Sasaki et al., 2013).

ECC and PDAC also have similar histochemical and immunohistochemical phenotypes. For example, both carcinomas frequently express and secrete neutral and acid mucin. Immunohistochemically, they express MUC1, MUC3, and MUC5/6 frequently, but not MUC2. Regarding their cytokeratin profile, normal pancreatic duct and bile duct cells express CK7 and 19, and PDAC and ECC express the same set of CKs as the normal duct epithelium. Carcinoembyronic antigen (CEA), carbohydrate antigen (CA)19-9 and Du-Pan 2 are also frequently expressed in both adenocarcinomas. Anterior gradient protein-2 and S100P are frequently expressed in ECC and PDAC, whereas neural cell adhesion molecule and the luminal expression of epithelial membrane antigen are uncommon in these carcinomas. PDX1 and HES1 are frequently and markedly expressed in PDAC and ECC, and also in their preneoplastic intraepithelial lesions (Ohshio et al., 1990; Igarashi et al., 2012).

Intraepithelial neoplastic epithelial lesions of the biliary tract and pancreas

Pancreatic intraepithelial neoplasm (PanIN) is known as a precursor to PDAC and shows microscopic intraepithelial proliferative changes (Hruban et al., 2010). PanINs are classified morphologically into three grades: PanIN-1, PanIN-2, and PanIN-3. PanINs, and particularly higher grade PanINs (PanIN-3), are more common in the pancreas with PDAC. CC is also reported to develop through multi-step carcinogenesis, and from pre-malignant or *in-situ* non-invasive neoplastic lesions in long-standing biliary diseases, particularly hepatolithiasis. Microscopic lesions of flat or low-papillary dysplastic epithelia have recently been proposed as biliary intraepithelial neoplasia (BilIN), in a similar fashion to PanIN, and are graded into BilIN-1, -2, and -3 (Zen et al., 2007; Nakanuma et al., 2010a,b).

BilIN and PanIN show similar histologies. In our previous studies, BilIN and PanIN showed similar

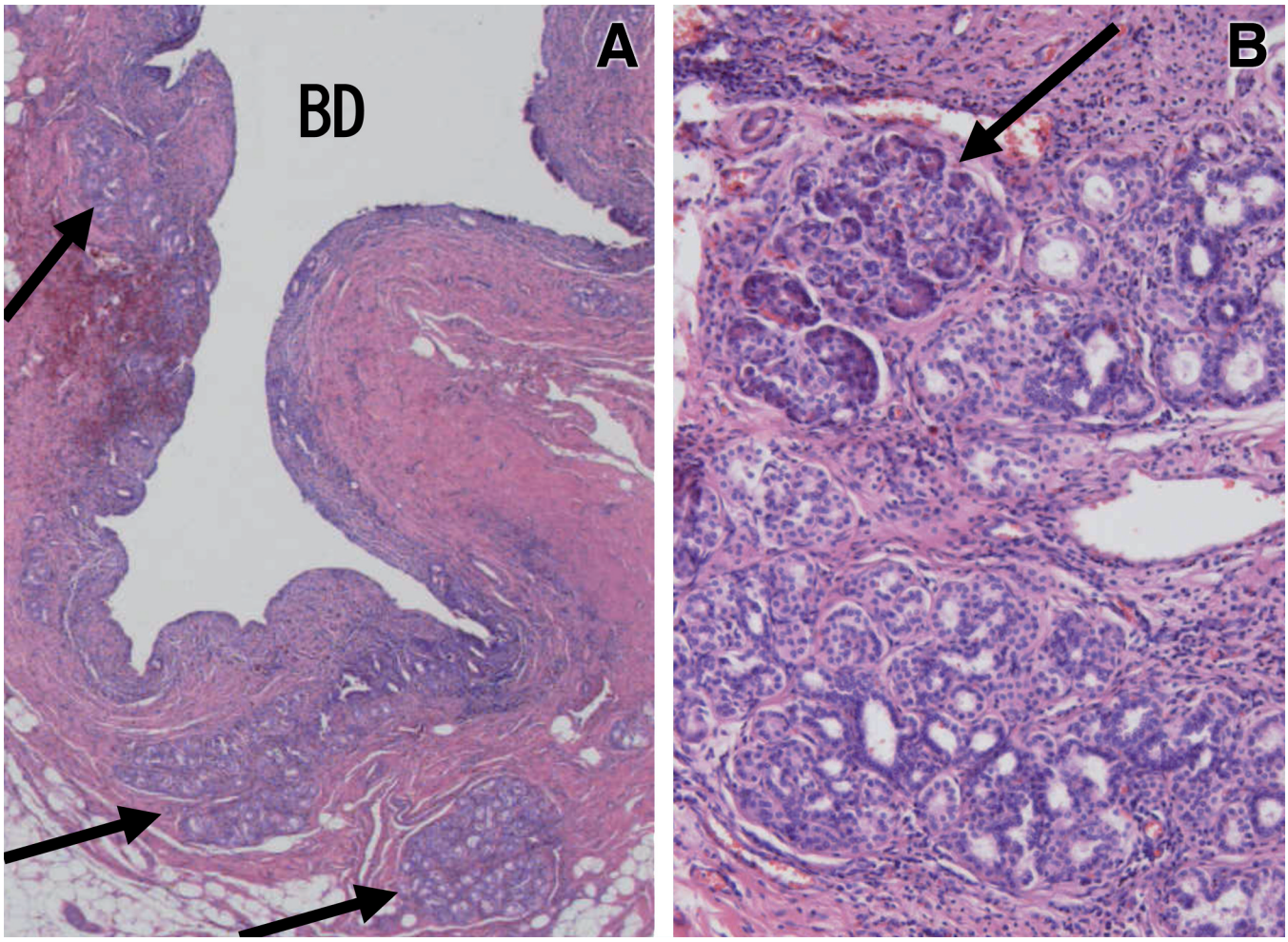

Fig. 1. Peribiliary glands of the hilar bile duct. **A.** Peribiliary glands (arrows) around the hilar bile duct (BD). HE. **B.** Extramural type of peribiliary glands contain acini of the exocrine pancreas (arrow). HE. A, x 10; B, x 150

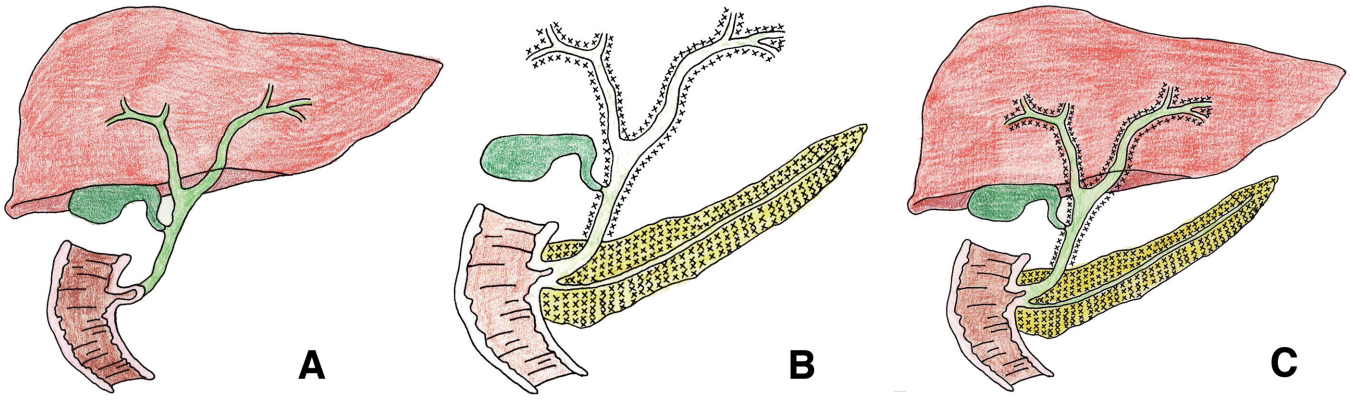

Fig. 2. Schematic presentation of the liver, biliary tract, pancreas, and papilla Vater. **A.** Biliary tract specialized for the drainage of bile secreted by hepatic parenchyma, particularly hepatocytes. **B.** Biliary tract specialized for drainage of products secreted by peribiliary glands. x means pancreatic elements in the pancreas and also in the peribiliary glands around the biliary tract. **C.** Composite of the biliary tract for the drainage of bile secreted by hepatic parenchyma and of products secreted by peribiliary glands.

expression patterns for mucin core proteins (MUC1 and MUC2) and cytokeratins (CK7 and CK20), which suggested that similar phenotypic changes may occur in both BilIN and PanIN.

Taken together, ECC and PDAC and their precursor lesions are similar to each other, and this suggests similar carcinogenic processes in the biliary tract and pancreas, followed by invasive lesions. PanINs and BilINs have also been found to be multifocal, which supports the above mentioned suggestion.

Table 1. Biliary diseases with pancreatic counterparts.

	Biliary Diseases	Pancreatic Diseases (Counterparts)
A. Neoplastic diseases		
1	Extrahepatic cholangiocarcinoma	Pancreatic duct adenocarcinoma
2	Biliary intraepithelial neoplasm (BilIN)	Biliary intraepithelial neoplasm (BilIN)
3	Intraductal papillary neoplasm of the bile duct (IPNB)	Intraductal papillary mucinous neoplasm (IPMN)
4	Intraductal tubular neoplasm (ITN)	Intraductal tubulopapillary neoplasm (ITPN)
5	Hepatic mucinous cystic neoplasm	Pancreatic mucinous cystic neoplasm
6	Hepatic serous neoplasm	Pancreatic serous neoplasm
B. Non-neoplastic diseases		
1	Peribiliary cysts and fibrosis in alcoholics	Pancreatic fibrosis and pancreatitis in alcoholics
2	IgG4-related sclerosing cholangitis	Autoimmune pancreatitis
3	Cystic fibrosis of the liver	Cystic fibrosis of the pancreas

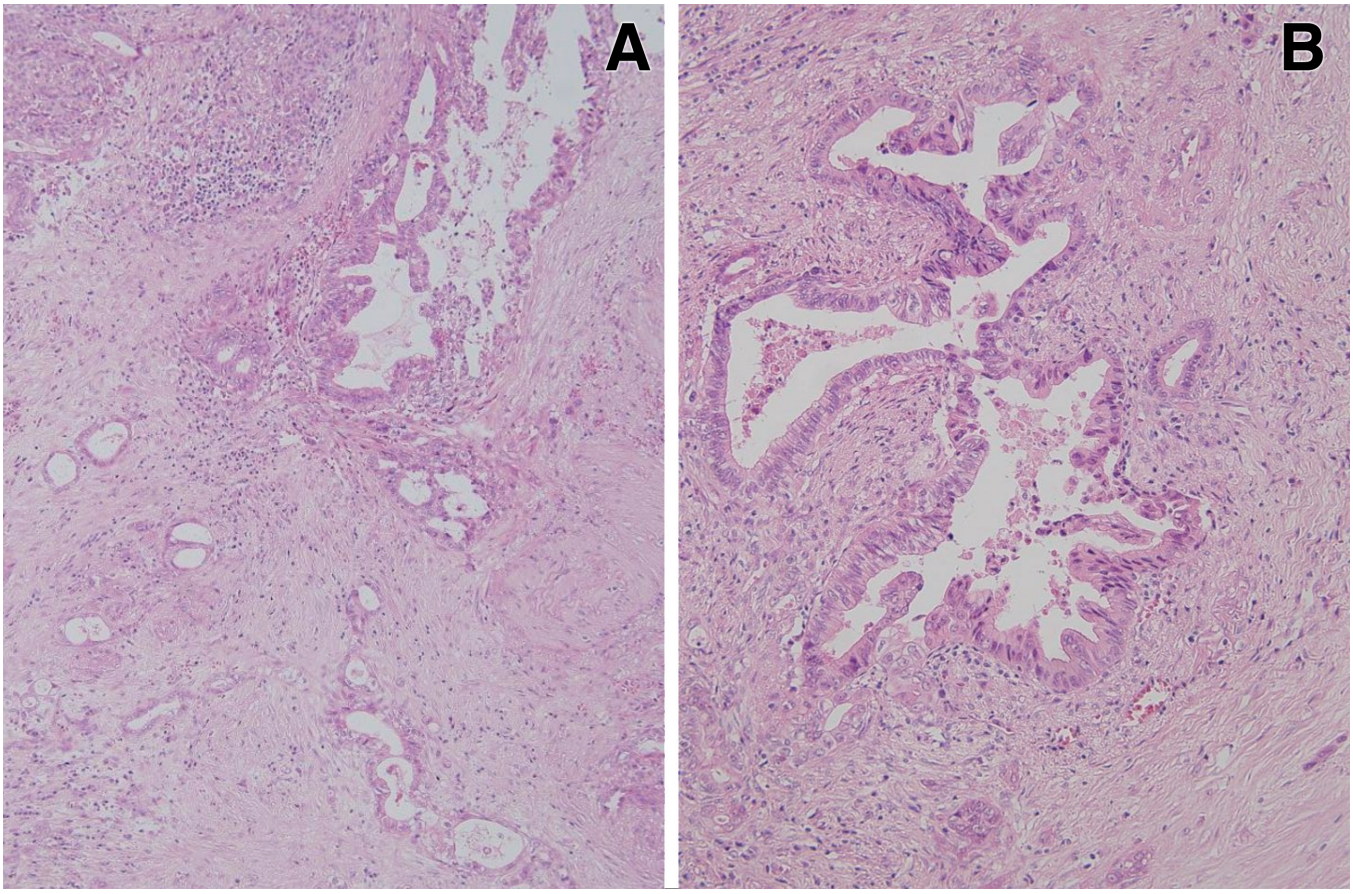

Fig. 3. Histologies of cholangiocarcinoma and pancreatic ductal adenocarcinoma (Gandou et al., 2013). **A.** Hilar cholangiocarcinoma (CC) showing tubular and micropapillary adenocarcinoma composed of columnar and cuboidal carcinoma cells with a desmoplastic reaction. HE. **B.** Pancreatic ductal adenocarcinoma showing a micropapillary pattern composed of columnar and tubular carcinoma cells with a desmoplastic reaction. HE. A, x 150; B, x 170.

Intraductal papillary neoplasm of the bile duct and pancreas

Intraductal tumors with grossly visible intraluminal papillary tumor(s) are known to develop in the pancreatic ducts (intraductal papillary mucinous neoplasm, IPMN) as well as in the biliary tract (intraductal papillary neoplasm of the bile duct, IPNB) (Adsay et al., 2010; Nakanuma et al., 2010a,b). IPMN and IPNB are composed of fine fibrovascular cores lined

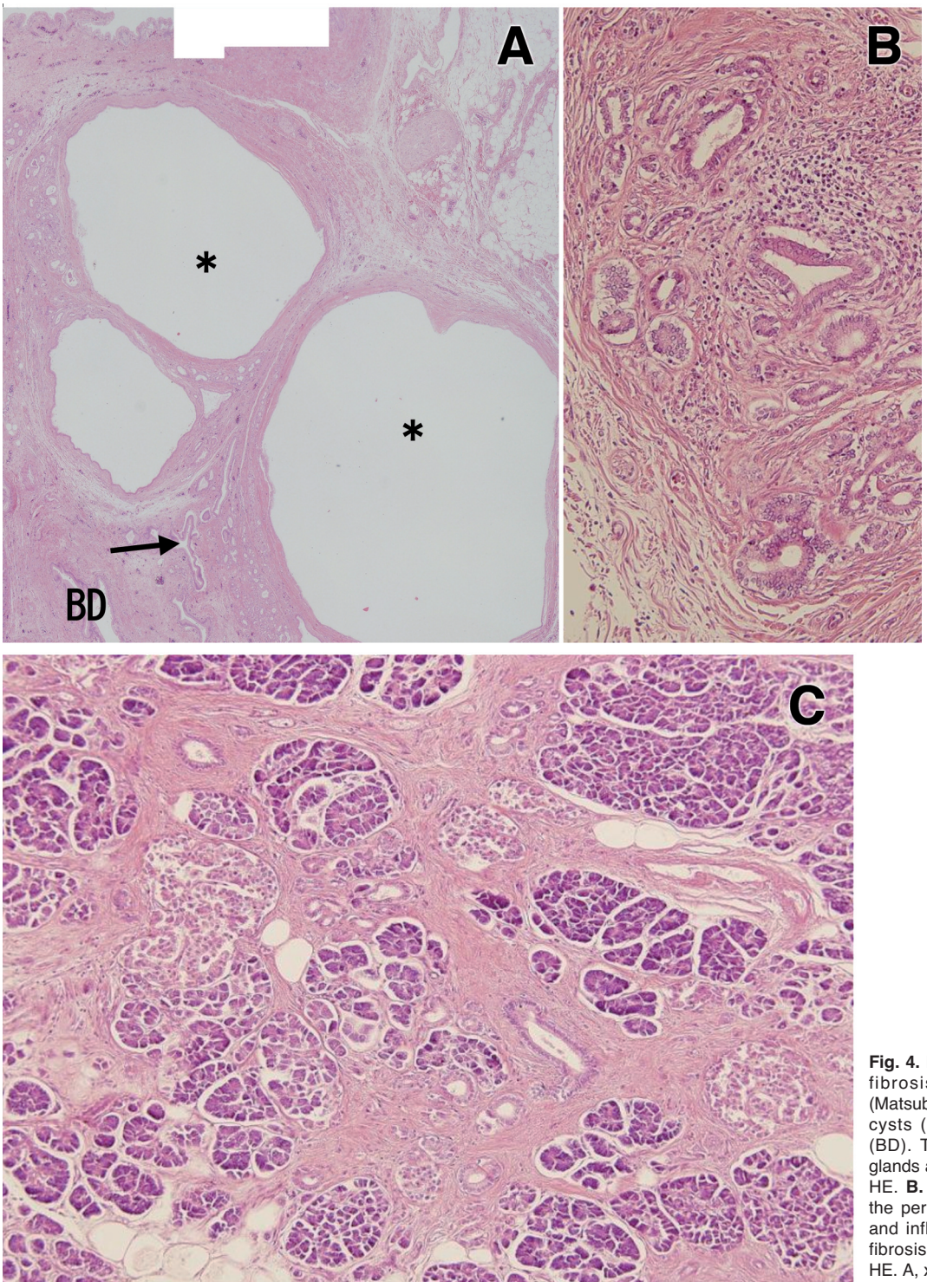

Fig. 4. Peribiliary cysts and pancreatic fibrosis in chronic alcoholics (Matsubara et al., 2013). **A.** Peribiliary cysts (*) around the hilar bile duct (BD). The arrow denotes peribiliary glands adjacent to the peribiliary cysts. HE. **B.** Peribiliary glands adjacent to the peribiliary cysts, showing fibrosis and inflammation. HE. **C.** Pancreatic fibrosis. Exocrine parts are atrophic. HE. A, x 10; B, x 150; C, x 100

by cuboidal to columnar neoplastic epithelial cells. Interestingly, the lining epithelia of IPNB and IPMN show either one or several of four phenotypes, such as "intestinal", "gastric (foveolar and pyloric)", "pancreatobiliary", and "oncocytic" epithelia. Mucin hypersecretion is frequently found in these tumors, particularly in IPMN. Densely cellular connective tissue resembling ovarian stroma (ovarian-like stroma) has not been observed in any cases of IPNB or IPMN.

IPNBs are histologically mainly well differentiated papillary adenocarcinoma and/or papillary epithelial borderline lesions, or adenomas as in main duct IPMN. IPNBs have been classified into three categories: i) low- or intermediate-grade dysplasia, ii) high-grade dysplasia, and iii) IPNB or IPMN with associated invasive carcinoma. The low- or intermediate-grade type belongs to adenomas or borderline lesions with mild cellular and nuclear atypia while the high-grade category includes in fact "pre-invasive" or "*in situ*" papillary adenocarcinoma with cellular/nuclear and structural atypia adequate enough for malignancy. Invasive parts of IPNB do not frequently contain mucinous carcinoma elements, while ordinary tubular adenocarcinoma is frequent (Nakanuma et al., 2010a,b).

Main duct IPMN and its biliary counterparts: The main pancreatic duct-type IPMN is typically diffusely dilated. The duct is often filled with mucin, and is tortuous and irregular. The affected bile ducts of IPNB showing variable fusiform dilatation, and occasionally cystic dilatation, resemble the main pancreatic duct-type IPMN. Their histological features are described above (Adsay et al., 2010).

Branch duct-type IPMN and its biliary counterparts: Branch duct-type IPMNs form multicystic, grape-like structures (Adsay et al., 2010). These cystically dilated ducts range from 1 to 8-10 cm and are filled with tenacious mucin. The cyst walls are usually thin, and can have either a flat or papillary lining. These lesions are also characterized by the intraductal proliferation of columnar mucin-producing cells, and the majority of this type are borderline or adenoma, and mainly present with a gastric phenotype (Adsay et al., 2010). So far, the biliary counterparts of branch duct-type IPMN remain speculative. Recently, IPNBs corresponding to branch duct-type IPMN have also been reported (Nakanuma and Sato, 2012), and this type is speculated to be derived from the peribiliary glands. Some cases only involve the peribiliary glands, while others involve the peribiliary glands and bile ducts. Cystic and micropapillary lesions involving the peribiliary glands present with gastric phenotypes, increased cell proliferative activities, and the expression of S100P, a marker of pancreatic neoplastic lesions. These lesions may also belong to a branch type-IPNB.

Intraductal tubular or papillotubular neoplasm of the bile duct and pancreas

Intraductal papillotubular neoplasm (ITPN) of the pancreas is defined as a grossly visible epithelial neoplasm within dilated pancreatic ducts that is composed of tubular glands without the significant formation of papillae (Adsay et al., 2010). Most reported ITPNs of the pancreas have minimal cytologic atypia, are composed of glands resembling pyloric glands, and are classified as ITPN with low grade dysplasia. ITPN with high-grade dysplasia (carcinoma in situ) and invasive carcinoma have also been reported. Intraductal tubular neoplasm (ITN) in the bile duct similar to pancreatic ITPN has also been recently reported (Katabi et al., 2012; Sato et al., 2012). These cases present with a predominantly tubular growth pattern, and show the foci of dysplasia and carcinoma *in situ* with histological features of the intestinal type with occasional goblet cells, while adenomatous foci were of the pyloric gland type. The intraductal portions of these tumors were densely cellular and composed of back-to-back tubular glands and solid sheets with minimal papillary architecture. The cells were cuboidal to columnar with mild to moderate cytologic atypia. ITN of the bile ducts could be a biliary counterpart of ITPN of the pancreas.

Mucinous cystic neoplasm of the bile duct and pancreas

Pancreatic mucinous cystic neoplasm (MCN) is characterized by "ovarian-type" hypercellular stroma, and their lining epithelium is single-layered columnar, mucin-producing cells (Zamboni et al., 2010). Such patients are relatively young and predominantly female. The cysts are lined by columnar epithelial cells positive for mucin. Recently, the WHO 2010 classification of tumors of the digestive system proposed that MCN of the liver is characterized by an underlying ovarian-type stromal component as proposed in MCN of the pancreas, and different from IPNB with variably luminal dilatation, occasionally cystic. Most reported cases of hepatic MCN had no luminal communication between the cystic tumor and bile duct. Stromal cells with the nuclear expression of ER or PgR were consistently observed in such biliary MCN as in pancreatic MCN. The clinical, histological, and biological behaviors of hepatobiliary MCN are similar to those of pancreatic MCN.

Serous neoplasm as seen in the pancreas (Terris et al., 2010) has also been occasionally reported in the liver. They may also belong to biliary diseases with pancreatic counterparts.

Non-neoplastic diseases of the biliary tract and pancreas showing similar pathological features and/or biological behaviors

Peribiliary cysts and pancreatic fibrosis in alcoholics

Peribiliary cysts or multiple hepatic hilar cysts are characterized by several to multiple grossly visible cystic lesions ranging in size from a few millimetres to 1 cm, and occasionally up to 3 cm, at the hepatic hilus or

perihilar regions. Peribiliary cysts are microscopically admixed with peribiliary glands, with variable dilatation of the peribiliary glands, and these cysts are therefore thought to originate in the peribiliary glands (Fig. 4A,B), though their exact histogenesis and pathogenesis has not been examined in detail.

Peribiliary cysts relate to pancreatic fibrosis in alcoholics

Routine experiences suggest that a history of heavy drinking is frequent in patients with peribiliary cysts, and peribiliary cysts are frequent in explant livers with alcoholic cirrhosis during liver transplantation (Nakanuma et al., 1984; Matsubara et al., 2013). For example, in our university hospital, a total of 11 out of 31 patients with peribiliary cysts had a history of heavy drinking, and all of these patients had alcoholic hepatitis/cirrhosis or alcoholic pancreatitis. A survey of our autopsy series showed that these cysts were found in 29 of 202 autopsy cases with a history of heavy drinking, and these cases were associated with alcoholic liver disease or alcoholic related pancreatic diseases. A PubMed search for peribiliary cysts revealed a total of 36 cases of peribiliary cysts in 26 references. Interestingly, among them, 15 cases were associated with alcoholic hepatitis/cirrhosis.

Peribiliary cysts are associated with adenitis of the peribiliary glands and pancreatic fibrosis

Pathologically, peribiliary cysts in chronic alcoholics have been frequently associated with necroinflammatory changes (adenitis) and fibrosis in the peribiliary glands. Interestingly, the degree of this adenitis with fibrosis has been closely associated with that of pancreatic fibrosis in alcoholics (Fig. 4C). Therefore, alcoholic injuries against the pancreatic acini and also against the peribiliary glands and exocrine pancreas may be followed by the development of adenitis, fibrosis, and cyst formation in the former and progressive fibrosis in the latter, respectively (Matsubara et al., 2013).

Peribiliary cysts have also been associated with alcoholic-related hepatic fibrosis, which suggests that alcoholic injuries to the hepatocytes with activation of hepatic stellate cells may also be related to peribliary cyst formation and fibrosis of the peribiliary glands.

In addition to the alcoholic contribution, other factors also lead to the development of peribiliary cirrhosis, such as chronic advanced liver diseases unrelated to alcoholic liver diseases and autosomal dominant polycystic kidney disease (ADPKD) (Kida et al., 1992).

IgG4-related disease of the biliary tract and pancreas: autoimmune pancreatitis and IgG4-related sclerosing cholangitis

Autoimmune pancreatitis (AIP) is characterized by marked lymphoplasmacytic infiltration with variable acinar atrophy and loss and also periductal infiltrates of lymphocytes and plasma cells of the pancreatic duct (Zen et al., 2004; Zhang et al., 2007; Deshpande et al., 2012). Additional characteristic features are also seen: (i) irregular or storiform fibrosis; (ii) extension of sclerosing and lymphoplasmacytic inflammation to parapancreatic adipose tissue; and (iii) obliterative phlebitis. More than 90% of patients with AIP have high serum IgG levels, particularly IgG4, and many IgG4+ plasma cells are evident immunohistochemically in the affected pancreas. This type of AIH has recently been named type 1 or lymphoplasmacytic pancreatitis and corresponds to the pancreatic manifestation of IgG4-related diseases (Zen et al., 2004; Zhang et al., 2007; Deshpande et al., 2012).

The biliary tract is frequently affected in patients with AIP and the affected biliary and pancreatic tissues show similar histopathology, such as the marked infiltration of lymphoplasma cells, including many IgG4 positive plasma cells, and fibrosis of the bile duct walls. Interestingly, obliterative phlebitis has also been seen as well as fibrosis (Zen et al., 2004). This type of sclerosing cholangitis (SC) is called IgG4-SC. Epithelial cells lining the affected large bile ducts appear to be spared in IgG4-SC as seen in the pancreatic duct in AIP. It is of interest that the peribiliary glands are more severely affected and inflammatory reactions are clearly oriented toward these glands, and these glands show epithelial damage and are destroyed (Nakanuma et al., 2011). Perineural lymphoplasmacytic infiltration and extension to the periductal connective tissue have been also reported in IgG4-SC, as is seen in AIP.

Proposal of a new disease concept of "biliary diseases with pancreatic counterparts"

The biliary tract involves two drainage systems: hepatic parenchyma and peribiliary glands

As mentioned above, the biliary tract appears to be involved in two drainage systems: the drainage duct system for the secretions of hepatic parenchyma, particularly hepatocytes (so-called bile), and that for secretions from the peribiliary glands (Ishida et al., 1989; Nakanuma, 2010). The biliary tract is commonly used by these two drainage systems, and the secretions of these two parts are mixed and drained into the lumen of the biliary tract and then into the duodenum via the papilla Vater: more importantly, the peribiliary glands retain some features of the pancreas such as exocrine pancreatic acini and the expression of pancreatic exocrine enzymes and Pdx1; therefore, it seems possible that the drainage complex of the peribiliary glands and biliary tract could be regarded as a sort of ectopic pancreas that works functionally and morphologically as a pancreas outside the proper pancreas (Fig. 2A-C) (Nakanuma, 2010).

Diseases affecting the exocrine acini and pancreatic

duct of the pancreas may develop in this pancreas of the biliary tract outside the proper pancreas, though the incidence of the latter may be lower than that of the pancreas itself, because the volume of exocrine acini and ducts is much larger in the pancreas itself than in the peribiliary glands and their complex.

Proposal of "biliary diseases with pancreatic counterparts"

Based on the pathologic similarities of the above mentioned biliary diseases to several pancreatic diseases, we have proposed a new concept "biliary diseases with pancreatic counterparts" for these diseases. They have been described above and also shown in Table 1. As neoplastic diseases, PDAC, ECC, and their precursor lesions (PanIN and BilIN), IPMN and IPNB (main duct type and branch type), ITPN or ITNB, and biliary and pancreatic MCN, and possibly pancreatic and hepatic serous neoplasms are also included in this category. As non-neoplastic diseases, IgG4-related diseases affect the pancreas and its ducts (autoimmune pancreatitis) and also affect the peribiliary glands and biliary tract (IgG4-related sclerosing cholangitis) in the same patients. Chronic alcoholic injuries affect the pancreas, followed by chronic pancreatitis and fibrosis, and also the peribiliary glands, followed by adenitis and fibrosis, and the development of peribiliary cysts.

Regarding the pathogenetic mechanisms of these biliary diseases with their pancreatic counterparts, the diseases that occur in the pancreas may also involve pancreatic elements of the biliary tree, therefore the pathological changes caused by these biliary diseases resemble those of their pancreatic counterparts, as mentioned above. So far, the majority of biliary and pancreatic diseases have been examined and studied separately, and the therapeutical strategies for biliary and pancreatic diseases have been discussed and applied, respectively. As described above, a more comprehensive and common analysis and approach to these biliary diseases and pancreatic counterparts are now available based on this new concept. Clinical and research data accumulated for pancreatic diseases could be applied to the analysis of biliary tract diseases and vice versa, and those patients with biliary tract diseases could receive efficient therapeutic approaches derived from the advances from pancreatic research and vice versa. For example, Furukawa et al reported that a GNAS mutation was found in 50% of IPMN of the pancreas (Furukawa et al., 2011); therefore, we attempted this approach in IPNB and we successfully detected a GNAS mutation in about half of IPNB patients (Sasaki et al. in submission). A survey of ITPN lesions as seen in the pancreas successfully revealed similar neoplasms in the biliary tract (Sata et al., 2010; Katabi et al., 2012). It is also interesting that pancreatic duct glands are now studied with reference to peribiliary glands (Strobel et al., 2010; Yamaguchi et al., 2011, 2012).

In conclusion, the conceptual and unified term "biliary diseases with pancreatic counterparts" has been proposed based on the findings that some pancreatic and biliary diseases share many similar pathological, histological, and immunohistochemical features in addition to clinical features. By this new disease concept, information obtained in disease(s) of the pancreas or biliary tract are applicable to analysis of counterpart diseases and vice versa, and further, novel therapeutical strategies and molecular and genetic studies on these diseases with a unified approach are warranted. In this context, novel approaches based on the new disease concept proposed here may be beneficial to patients with biliary tract and also pancreatic diseases.

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