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Biliary tumors with pancreatic counterparts

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ABSTRACT

Some biliary diseases mimic pancreatic diseases pathologically as well as pathogenetically. Such diseases can be called "biliary diseases with pancreatic counterparts". Biliary intraepithelial neoplasm (BilIN), intraductal papillary neoplasm of bile ducts (IPNB), hepatobiliary mucinous cystic neoplasm (hMCN), and IgG4-inflammatory pseudotumor represent the biliary counterparts of pancreatic intraepithelial neoplasm (PanIN), intraductal papillary mucinous neoplasm of pancreas (IPMN), pancreatic MCN, and mass forming type 1 autoimmune pancreatitis (AIP), respectively. BilIN and PanIN represent pre-invasive intraepithelial stages of nodular sclerosing cholangiocarcinoma and pancreatic ductal adenocarcinoma, respectively. IPNB and IPMN are grossly visible, predominant papillary, intraductal neoplasms that may progress to invasive carcinoma. Morphologically similar MCNs with subepithelial ovarian-like stroma occur in both the hepatobiliary system as well as the pancreas. IgG4-inflammatory pseudotumor, usually of the lymphoplasmacytic type, and mass forming type 1 AIP represent IgG4-related disease in the biliary tree and pancreas respectively. The biliary tract, which is associated with the peribiliary glands, including the pancreatic acini, can be regarded as an incomplete pancreas, so several diseases mimicking pancreatic diseases may be expected to occur in the biliary tract (biliary diseases with pancreatic counterparts).

Introduction

It is well recognized that several non-neoplastic and neoplastic biliary diseases resemble pancreatic diseases.[1–3] For example, IgG4-related disease demonstrating markedly similar histologic features frequently occurs simultaneously or metachronously in the biliary tract (IgG4-related sclerosing cholangitis [IgG4-SC]) and pancreas (type 1 autoimmune pancreatitis [type I AIP]).[1,4] Mucinous cystic neoplasms (MCNs) with ovarian-like stroma occur in the hepatobiliary system as well as in the pancreas.[5] Why do these biliary and pancreatic diseases present similar or identical features?

The biliary tract and pancreas are anatomically closely located and connected to each other and share important physiological functions.[1–3] Both derive almost simultaneously from the foregut endoderm; the ventral pancreas derives from the common bile duct during development, suggesting that pancreatic tissue can be present in the extrahepatic bile ducts near the ventral pancreas. Subsequently, the ventral pancreas revolves clockwise with the common bile duct to unite with the dorsal pancreas. Interestingly, the epithelia lining the bile duct and main pancreatic duct are both simple columnar epithelia and exhibit similar reactive changes during pathologic conditions; furthermore, both are accompanied by periductal glands, the peribiliary glands and pancreatic duct glands, respectively.[6,7] Many transcriptional factors, such as Hes1, PDX1, and Neurog3, are commonly involved in development of the pancreas and biliary tract.[1] Hes1 represses the expression of Neurog3, a promoter of pancreatic exocrine and endocrine differentiation. Interestingly, in Hes1-knockout mice, the bile ducts express Neurog3 ectopically and transform into pancreatic exocrine cells. In humans, the peribiliary glands are located around the biliary tract and drain into the bile duct lumen via their own conduits.[6,8] Interestingly, small amounts of pancreatic exocrine acini are intermingled with the peribiliary glands (Fig. 1A and B), raising the possibility that these glands may be remnants of the developing ventral pancreas and bile ducts. Multipotent endodermal stem/progenitor cell populations along the biliary tract and pancreatic duct, particularly in the peribiliary glands and pancreatic duct glands,[9] have been identified; these cells are able to differentiate into cholangiocytes, hepatocytes, and pancreatic cells, suggesting that bile ducts may have the potential for pancreatic exocrine and even islet-like cell differentiation.[9] Based on these findings, it seems plausible that the biliary tract functions as a duct for the peribiliary glands with inherent pancreatic features or properties (incomplete pancreas) in addition to being a duct

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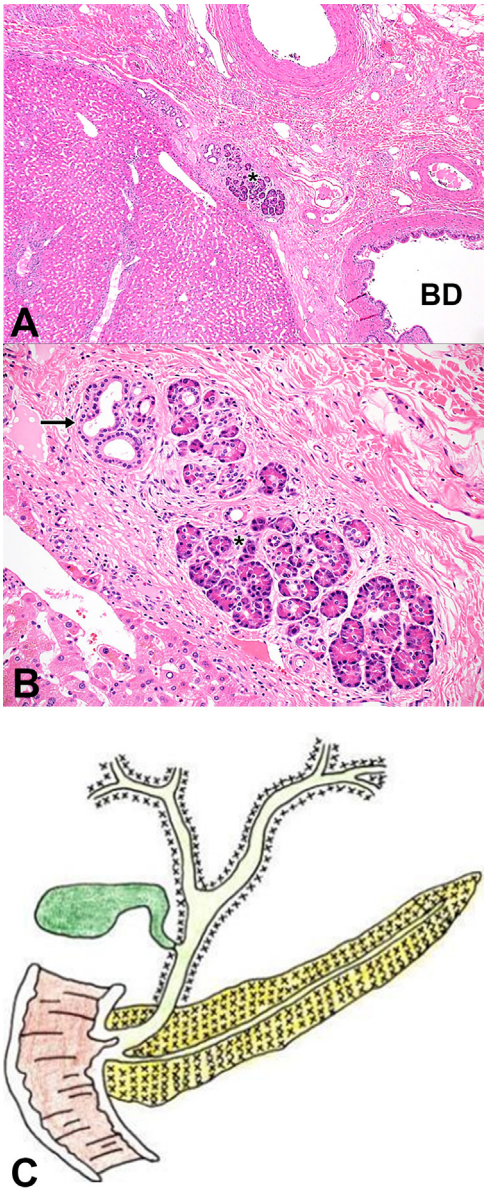

Fig. 1. Pancreatobiliary axis. Around the hilar bile duct (BD), there are peribiliary glands (A, asterix). At higher magnification, there are occasionally pancreatic exocrine acini (asterix) intermingled with other components of the peribiliary glands (B, arrow). A schematic presentation of the biliary tree with the peribiliary glands (asterix) and pancreas (asterix) (C). The bile duct is involved in the drainage of secretions from the peribiliary glands as well as that (bile) from hepatocytes. The bile ducts attached to the peribiliary glands can be regarded as an "incomplete pancreas", and this "incomplete pancreas" and pancreas itself form an axis. Thus, it seems conceivable that some pancreatic diseases can also develop along the biliary tree with the peribiliary glands.

system specialized for the drainage of bile secreted by the hepatic parenchyma. In this context, the biliary tract with the peribliary glands and the pancreas forms a kind of pancreatobiliary axis (Fig. 1C).

It is thus not surprising that non-neoplastic and neoplastic biliary diseases exhibit similarities to corresponding pancreatic diseases, thus justifying the concept of "biliary diseases with pancreatic counterparts".[1–3] The incidence of such biliary diseases is however lower in comparison to their pancreatic counterparts, as the volume of the peribiliary glands is much smaller than that of the pancreas itself, and their histologies may not be exactly the same.[1–3] This article reviews four biliary diseases which bear strong resemblance to similar pancreatic diseases (Table 1).

Table 1
Biliary tumors with pancreatic counterparts.

Biliary neoplasm	Pancreatic counterpart
Biliary intraepithelial neoplasm (BilIN)	Pancreatic intraepithelial neoplasm (PanIN)
Intraductal papillary neoplasm of bile duct (IPNB)	Intraductal papillary mucinous neoplasm (IPMN)
Hepatobiliary mucinous cystic neoplasm	Pancreatic mucinous cystic neoplasm
IgG4-inflammatory pseudotumor of the liver	Mass-forming type I autoimmune pancreatitis

Case 1

A 62-year-old male was admitted to our hospital with complaints of upper abdominal pain. A diagnosis of intrahepatic cholangiocarcinoma (CCA) associated with hepatolithiasis in the left hepatic lobe was made, and left lobectomy was performed.

Pathologic findings

The nodular sclerosing tumor involved mainly the large left intrahepatic duct which contained stones. It was histologically a moderately differentiated tubular adenocarcinoma with desmoplastic reaction that had invaded the periductal tissues. In the bile ducts around the main tumor, foci or fields of intraepithelial preinvasive neoplastic lesions were microscopically found (Fig. 2A). They showed nuclear stratification and hyperchromasia with occasional nuclear pile-up to the luminal surface. Some areas were regarded as BilIN-3 (*in situ* carcinoma) showing disordered nuclear polarity and nuclear anisocytosis (Fig. 2A and B), while other parts were regarded as BilIN-1/2 (low-/intermediate-grade lesion) (Fig. 2C). While the cellular, nuclear, and structural atypia of BilINs were mild in comparison with those of the invading carcinoma of the main tumor, all-grade BilINs and the invading carcinoma of the main tumor were strongly positive for S100P (Fig. 2B, inset). Nuclear expression of p53 was scattered in the BilIN lesions, but was strongly and diffusely positive in at least some areas of invasive CCA. Other parts of the bile ducts showed proliferation of the peribiliary glands with fibrosis and infiltration by inflammatory cells (chronic proliferative cholangitis) related to hepatolithiasis.

Diagnosis: Intrahepatic cholangiocarcinoma with biliary intraepithelial neoplasia and hepatolithiasis

Discussion

BilINs represent flat, premalignant intraepithelial neoplasia of the bile ducts that are recognizable under a microscope as an atypical intraepithelial proliferation that shows multilayering of nuclei and flat or micropapillary projections into the duct lumen.[10,11] The nuclei are round or oval, and their sizes are slightly larger or smaller than those of epithelial cells lining adjacent non-neoplastic large bile ducts. Atypical cells have an increased nucleus-to-cytoplasm ratio, partial loss of nuclear polarity, and nuclear hyperchromasia. BilINs usually occur as a field effect or as multiple foci in the extrahepatic and large intrahepatic bile ducts. The lesion may extend into the associated peribiliary glands. BilIN may also occur in the gallbladder.[1–3,10,11]

BilINs are regarded as a pre-invasive lesions of nodular sclerosing (NS)-CCA.[10,11] They are usually strongly positive for CK7, a marker of biliary epithelial cells, although some foci are also simultaneously positive for CK20, and some show intestinal metaplasia characterized by intestinal villi or goblet cells. BilIN has been mainly studied in the intrahepatic large bile ducts and perihilar bile ducts of individuals with chronic biliary diseases, particularly