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REVIEW

Pancreaticobiliary maljunction and biliary cancer

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Abstract Pancreaticobiliary maljunction (PBM) is a congenital malformation in which the pancreatic and bile ducts join anatomically outside the duodenal wall. Japanese clinical practice guidelines on how to deal with PBM were made in 2012, representing a world first. According to the 2013 revision to the diagnostic criteria for PBM, in addition to direct cholangiography, diagnosis can be made by magnetic resonance cholangiopancreatography (MRCP), 3-dimensional drip infusion cholangiography computed tomography, endoscopic ultrasonography (US), or multiplanar reconstruction images by multidetector row computed tomography. In PBM, the common channel is so long that sphincter action does not affect the pancreaticobiliary junction, and pancreatic juice frequently refluxes into the biliary tract. Persistence of refluxed pancreatic juice injures epithelium of the biliary tract and promotes cancer development, resulting in higher rates of carcinogenesis in the biliary tract. In a nationwide survey, biliary cancer was detected in 21.6 % of adult patients with congenital biliary dilatation (bile duct cancer, 32.1 % vs. gallbladder cancer, 62.3 %) and in 42.4 % of PBM patients without biliary dilatation (bile duct cancer, 7.3 % vs. gallbladder cancer, 88.1 %). Pathophysiological conditions due to pancreatobiliary reflux occur in patients with high confluence of pancreaticobiliary ducts, a common channel ≥6 mm long, and occlusion of communication during contraction of the sphincter. Once the diagnosis of PBM is established, immediate prophylactic surgery is recommended. However, the surgical strategy for PBM without biliary dilatation remains controversial. To detect PBM without biliary dilatation early, MRCP is recommended for patients showing gallbladder wall thickening on screening US under suspicion of PBM.

Keywords Pancreaticobiliary maljunction · Congenital biliary dilatation · Gallbladder cancer · Bile duct cancer

Introduction

Pancreaticobiliary maljunction (PBM) is a congenital malformation in which the pancreatic and bile ducts join anatomically outside the duodenal wall. The sphincter of Oddi is normally located at the distal end of the pancreatic and bile ducts and regulates the outflow of bile and pancreatic juice. In PBM, the common channel is so long that action of the sphincter of Oddi does not directly affect the pancreaticobiliary junction. As a result, reciprocal reflux of pancreatic juices and bile occurs. As the fluid pressure in the pancreatic duct usually exceeds that in the bile duct, reflux of pancreatic juice into the biliary tract frequently occurs in PBM. Persistence of refluxed pancreatic juice injures the epithelium of the biliary tract and promotes cancer development, resulting in higher rates of

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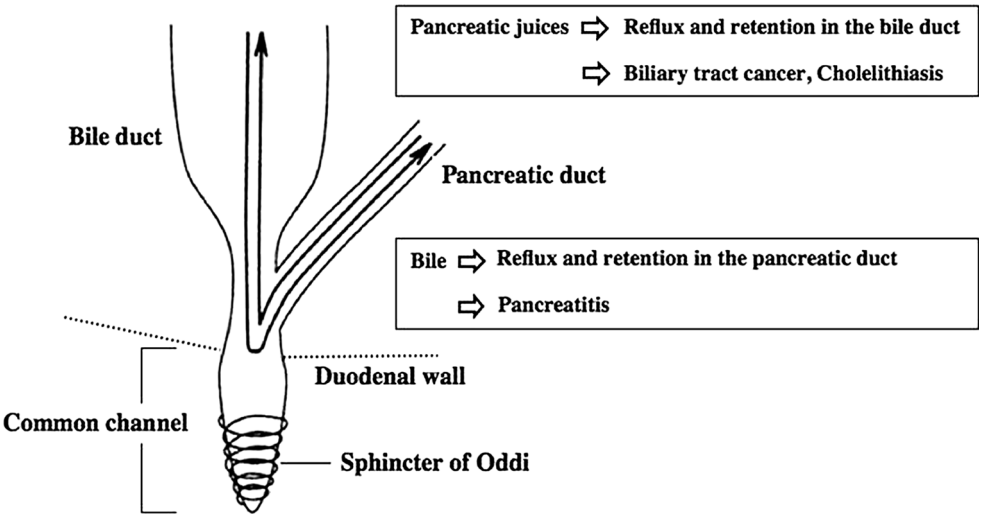

Fig. 1 The pathophysiology of pancreaticobiliary maljunction [3]

carcinogenesis in the biliary tract of PBM (Fig. 1). PBM can be divided into PBM with biliary dilatation (congenital biliary dilatation) and PBM without biliary dilatation [1, 2].

Japanese clinical practice guidelines on how to deal with PBM were created in 2012, as the first in the world [3]. Diagnostic criteria for PBM were revised in 2013, taking recent advances in diagnostic imaging techniques into consideration [4]. Based on the guidelines and new diagnostic criteria, we describe herein recent topics and problems in the management of PBM, with a focus on biliary cancer.

Diagnostic criteria for PBM 2013

Diagnostic criteria of PBM were proposed in 1987 [5], and were slightly revised in 1990 and published in English in 1994 [6]. In 2013, these criteria underwent thorough revision, 23 years to the day since the previous version (Table 1) [4]. Although no significant changes have been made to the definition of PBM, diagnostic modalities have undergone substantial advances in recent years. As no radiological modalities were initially available that could show the status of the pancreaticobiliary junction outside the duodenal wall, PBM was diagnosed when a lack of effect of the sphincter of Oddi on the pancreaticobiliary junction was verified on direct cholangiography such as with endoscopic retrograde cholangiopancreatography (ERCP).

Magnetic resonance cholangiopancreatography (MRCP) has now become popular as a noninvasive method for obtaining high-quality images of the pancreaticobiliary tree, and it is replacing diagnostic ERCP for many pancreatobiliary diseases. Many PBM cases can be diagnosed from MRCP based on findings of an anomalous union between the common bile duct and pancreatic duct in addition to a long common channel [7–10]. MRCP is thus useful for diagnosing children and screening for PBM [7]. However, accurate diagnosis of PBM is difficult in cases with a relatively short common channel (Fig. 2a, b) [11]. In cases with a common channel $\leq$9 mm on MRCP, direct cholangiography is needed to confirm PBM [12]. PBM can be diagnosed if junction outside the wall can be depicted by high-resolution images with multiplanar reconstruction (MPR) provided by multidetector row computed tomography (MD-CT), and endoscopic ultrasonography (EUS) [3, 13, 14].

Amylase levels in bile are markedly elevated (>10,000 IU/l) in most cases of PBM, but are not elevated at all in some cases [15, 16]. Furthermore, elevation of pancreatic enzyme levels in bile and hyperplastic changes to the gallbladder mucosa are sometimes observed in some cases with a relatively long common channel in which the effect of the sphincter reaches the pancreaticobiliary junction (high confluence of pancreaticobiliary ducts) [17–19].

Since the maximum diameter of the common bile duct correlates positively with age, standard values for the maximum diameter of the common bile duct in each age group appear appropriate for accurate evaluation of the presence of bile duct dilatation [20–22].

Biliary cancer associated with PBM

Incidence and characteristics

Biliary cancers are frequently observed in adult patients with PBM [23–25]. According to a nationwide survey in

Table 1 Diagnostic criteria for pancreaticobiliary maljunction 2013[4)]

I. Definition

Pancreaticobiliary maljunction is a congenital malformation in which the pancreatic and bile ducts join anatomically outside the duodenal wall.

II. Pathophysiology

In pancreaticobiliary maljunction, the duodenal papillary sphincter (sphincter of Oddi) fails to exert any influence on the pancreaticobiliary junction due to the abnormally long common channel. Therefore, reciprocal reflux between pancreatic juice and bile occurs, resulting in various pathologic conditions, such as inhibiting the excretion of bile and pancreatic juice, and biliary cancer, in the biliary tract and pancreas.

III. Diagnostic criteria

Pancreaticobiliary maljunction is diagnosed by either imaging test or anatomical examination.

Imaging diagnosis

a) An abnormally long common channel and/or an abnormal union between the pancreatic and bile ducts must be evident on direct cholangiography, such as endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transpehatic cholangiography (PTC), or intraoperative cholangiography; magnetic resonance cholangiopancreatography (MRCP); or three-dimensional drip infusion cholangiography computed tomography (3D-DIC-CT). However, in cases with a relatively short common channel, it is necessary to confirm that the effect of the papillary sphincter does not extend to the junction by direct cholangiography.

b) Pancreaticobiliary maljunction can be diagnosed if the pancreaticobiliary junction outside the wall can be depicted by endoscopic ultrasonography (EUS) or multi-planar reconstruction (MPR) images provided by multi-detector row computed tomography (MD-CT).

Anatomical diagnosis

It should be confirmed by surgery or autopsy that the pancreaticobiliary junction lies outside the duodenal wall, or pancreatic and bile ducts unite abnormally.

IV. Supplementary diagnosis

The following findings strongly suggest the existence of pancreaticobiliary maljunction.

Elevated amylase levels in bile

Pancreatic enzymes, especially amylase, in the bile within the bile duct and gallbladder obtained immediately after laparotomy, endoscopically or percutaneously are generally at extremely high levels. However, levels close to or below the normal serum value are occasionally observed in patients with pancreaticobiliary maljunction.

Clinical features similar to pancreaticobiliary maljunction, including elevation of pancreatic enzymes in bile, are observed in some cases with a relatively long common channel, showing the effect of the sphincter on the pancreaticobiliary junction.

Extrahepatic bile duct dilatation

Pancreaticobiliary maljunction includes one type that is associated with bile duct dilatation (congenital biliary dilatation), and another that is not (pancreaticobiliary dilatation without biliary dilatation). When cystic, fusiform, or cylindrical dilatation is detected in the extrahepatic bile duct, careful investigations are needed to determine whether pancreaticobiliary maljunction is present.

Standard values for the maximum diameter of the common bile duct at each age are useful for diagnosing pancreaticobiliary maljunction with or without biliary dilatation.

Japan ($n = 2561$) [2], biliary cancer was detected in 21.6 % of adult patients with congenital biliary dilatation and in 42.4 % of PBM patients without biliary dilatation. In patients with biliary cancers in association with PBM, the location ratio of cancers in the bile duct and gallbladder were 32.1 % and 62.3 % in congenital biliary dilatation, and 7.3 % and 88.1 % in PBM patients without biliary dilatation, respectively. The mean age at which PBM patients developed biliary cancer was 60.1 years for gallbladder cancer and 52.0 years for bile duct cancer among patients with congenital biliary dilatation, and 58.6 years for gallbladder cancer in PBM patients without biliary dilatation. Such patients develop biliary cancers 15–20 years earlier than patients without PBM [26].

In PBM patients, biliary cancers frequently develop as simultaneous and/or metachronous double cancers. Of 37 patients with simultaneous double or multiple biliary cancers, 19 patients (51 %) suffered from concurrent PBM [3, 27–31].

The ratio of gallstone detection in PBM patients who developed gallbladder cancer was lower than that in the biliary cancer population without PBM [2, 3, 32]. In our series, the ratios were 10 % and 62 %, respectively [1].

Mechanism of biliary carcinogenesis

The mechanisms of carcinogenesis in PBM appear to be related to the persistence of refluxed pancreatic juice into the biliary tract. Refluxed proteolytic pancreatic enzymes and phospholipase A2 are activated in the biliary tract and strongly cytotoxic substances such as lysolecithin are produced. The resulting chronic inflammation provokes repeated cycles of damage and healing in the biliary mucosal epithelia. These alterations in the mucosal epithelia, in conjunction with DNA mutations, finally promote cancer development and progression (Fig. 3) [1, 3, 33, 34]. The sequence of hyperplasia-dysplasia-carcinoma, regarded as the prevailing mechanism underlying the development of biliary tract cancer in PBM, is thought to differ from both the adenoma-carcinoma sequence and de novo carcinogenesis associated with biliary tract cancer in the population without PBM [35–37].

In our series, the gallbladder mucosa was significantly higher in PBM than in controls. The incidence of epithelial hyperplasia of the gallbladder and the Ki-67 labeling index of the gallbladder epithelium were significantly higher in PBM than in controls. K-ras mutations in the noncancerous epithelium of the gallbladder were detected in 36 % of PBM patients [1, 19]. Considering that increased cell proliferation is linked to the development of cancer by means of tumor promotion and an increased rate of random mutations, the gallbladder mucosa of PBM patients can be considered to represent a premalignant region.

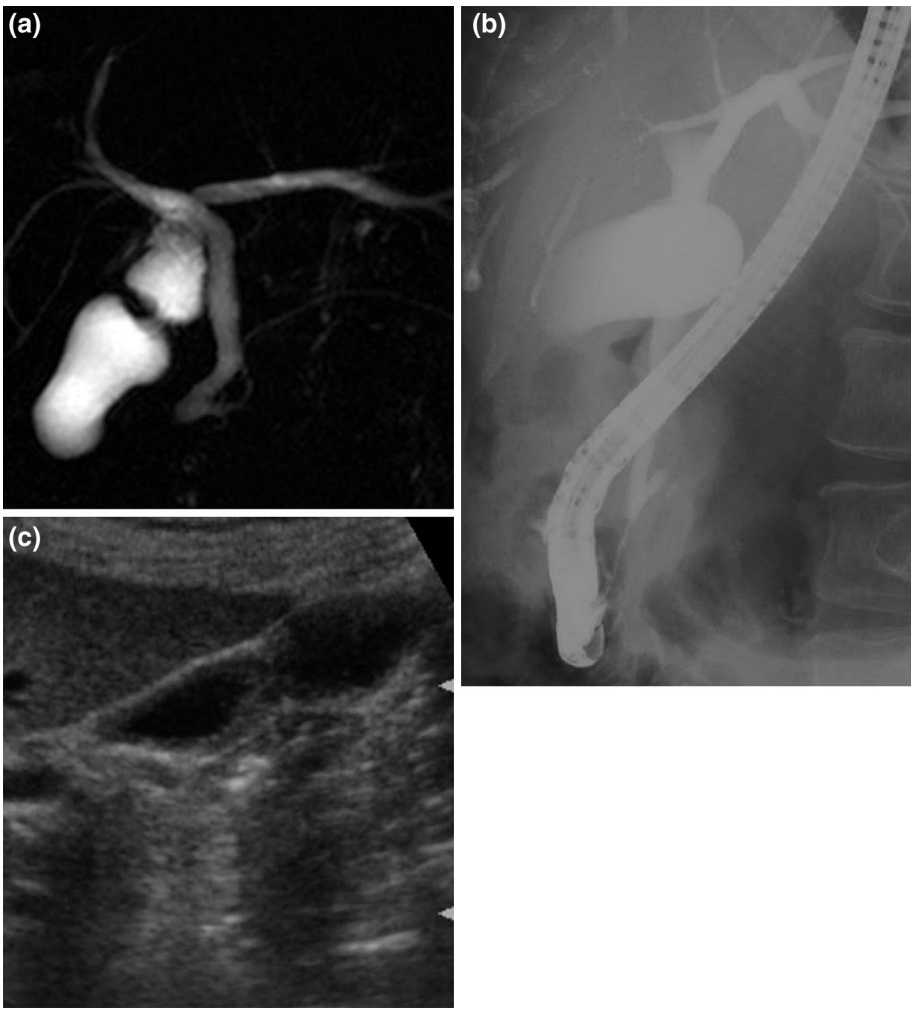

Fig. 2 Pancreaticobiliary maljunction without biliary dilatation was suspected by magnetic resonance cholangiopancreatography (MRCP) (**a**) and confirmed on endoscopic retrograde cholangiopancreatography (ERCP) (**b**). Ultrasonography in this patient showed gallbladder wall thickening (**c**)

Treatment of PBM

Once a diagnosis of PBM has been established, immediate prophylactic surgery is recommended before the onset of malignant changes. Cholecystectomy and resection of the extrahepatic bile duct (flow-diversion surgery) is an established standard for the surgical treatment of congenital biliary dilatation [3, 22]. Internal drainage operations have been abandoned because of the high risk of postoperative carcinogenesis.

On the other hand, treatment of PBM without biliary dilatation and without cancer is controversial. Prophylactic cholecystectomy is performed in many institutes, as most biliary cancers that develop in PBM patients without biliary dilatation are gallbladder cancers [38, 39]. However, some surgeons propose excision of the extrahepatic bile duct together with the gallbladder for PBM patients without biliary dilatation [23], because the frequency of bile duct cancer in PBM patients without biliary dilatation is higher compared to that in the general population [2], and K-ras and/or p53 gene mutations are also reportedly seen in the bile duct of PBM patients without biliary dilatation [23, 40].

Strategy for early diagnosis of PBM

Compared to congenital biliary dilatation, PBM cases without biliary dilatation rarely evoke symptoms, and most patients are not diagnosed until the onset of advanced stage gallbladder cancer [1, 38]. Detecting PBM before the development of biliary cancer is important in order to allow for prophylactic surgery. Epithelial hyperplasia of the gallbladder induced by longstanding continuous stasis of the bile intermingled with refluxed pancreatic juice is a characteristic pathological change in PBM patients [41–43]. To achieve early detection of PBM without biliary dilatation, MRCP is warranted in patients showing thickening of the gallbladder wall on screening US under suspicion of PBM (Fig. 2c) [44].

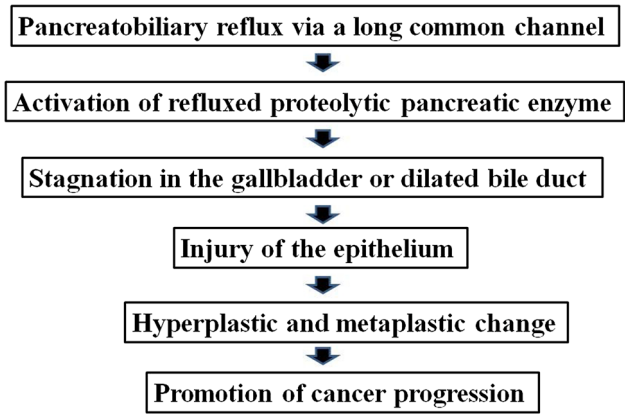

Fig. 3 Mechanism of biliary carcinogenesis in pancreaticobiliary maljunction [1]

High confluence of pancreaticobiliary ducts

The frequency of common channel formation ranges from 55 % to 91 % [17], and the mean length of the common channel has been reported as 4.5 mm [45]. To investigate the clinical significance of a relatively long common channel, we defined high confluence of pancreaticobiliary ducts (HCPBD) as a disease state in which the common channel length is ≥6 mm and communication is occluded when the sphincter of Oddi is contracted (Fig. 4a, b) [17].

In our series of 95 HCPBD patients, reflux of contrast medium into the pancreatic duct was detected in 86 % of patients who underwent postoperative T-tube cholangiography. Elevated amylase levels in bile were observed in all patients, although the mean levels were significantly lower than those in PBM patients. Gallbladder cancer was identified in 11 HCPBD patients (12 %). Similar to PBM patients, hyperplastic changes with increases in both the proliferative activity of epithelial cells and K-ras mutations were also detected in the noncancerous epithelium of the gallbladder in HCPBD patients [1, 18, 19]. A relatively long common channel also appears to represent an important risk factor for the development of gallbladder cancer. However, several differences exist between HCPBD and PBM without biliary dilatation in terms of other features, such as gender predilections, age at diagnosis, incidence of concomitant gallbladder cancer, and biliary amylase levels. HCPBD appears to represent an intermediate clinical condition that is both morphologically and functionally difficult to differentiate clearly from PBM. We consider that HCPBD should currently be managed as a disease entity independent of PBM in terms of the appropriate therapeutic strategies [1, 22].

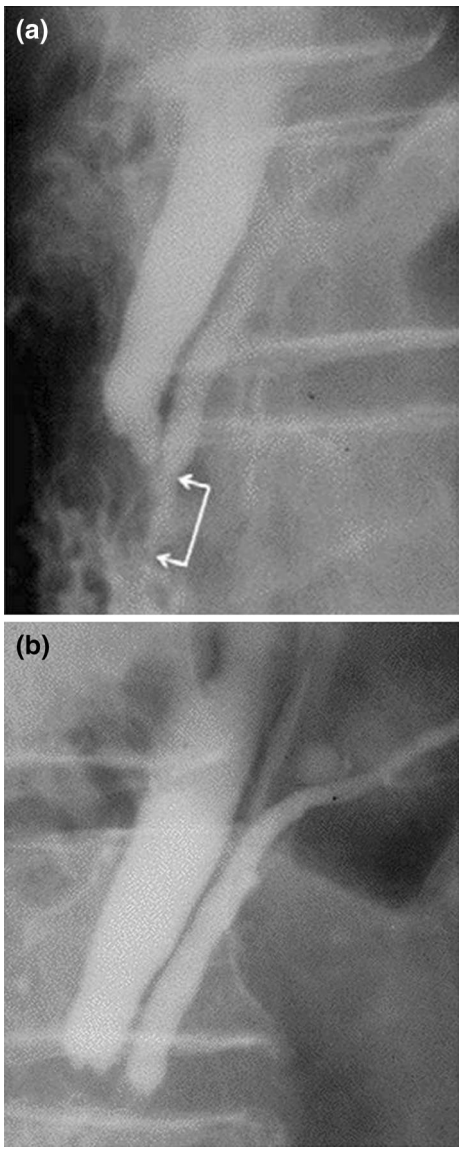

Fig. 4 Images from endoscopic retrograde cholangiopancreatography of high confluence of pancreaticobiliary ducts (HCPBD) [3]. The bile and pancreatic ducts form a common channel (*arrows*) 8 mm long during sphincter relaxation (**a**). Communication between these two ducts is interrupted during contraction of the sphincter of Oddi (**b**)

Conclusions

Biliary cancers occur frequently through proliferative processes provoked by chronic inflammation resulting from the persistence of pancreatic juice refluxed through a long common channel. Once PBM is diagnosed, immediate prophylactic surgery is recommended before malignant changes develop. It is important to diagnose PBM before the onset of biliary carcinogenesis. To achieve early detection of PBM without biliary dilatation, MRCP is recommended for patients showing gallbladder wall thickening on screening US under suspicion of PBM. Further investigations and surveillance studies are also needed to clarify appropriate surgical strategies for PBM without biliary dilatation.

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