Pancreaticobiliary reflux as a high-risk factor for biliary malignancy: Clinical features and diagnostic advancements

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Abstract

Pancreaticobiliary junction is composed of complex structure with which biliary duct and pancreatic duct assemble and go out into the ampulla of Vater during duodenum wall surrounding the sphincter of Oddi. Although the sphincter of Oddi functionally prevents the reflux of pancreatic juice, pancreaticobiliary reflux (PBR) occurs when function of the sphincter of Oddi halt. The anatomically abnormal junction is termed pancreaticobiliary maljunction (PBM) and is characterized by pancreatic and bile ducts joining outside of the duodenal wall. PBM is an important anatomical finding because many studies have revealed that biliary malignancies are related due to the carcinogenetic effect of the pancreatic back flow on the biliary mucosa. On the other hand, several studies have been published on the reflux of pancreatic juice into the bile duct without morphological PBM, and the correlation of such cases with biliary diseases, especially biliary malignancies, is drawing considerable attention. Although it has long been possible to diagnose PBM by various imaging modalities, PBR without PBM has remained difficult to assess. Therefore, the pathological features of PBR without PBM have not been yet fully elucidated. Lately, a new method of diagnosing PBR without PBM has appeared, and the features of PBR without PBM should soon be better understood.

Key words: Pancreaticobiliary maljunction; Pancreas juice; Reflux; Flow; Magnetic resonance imaging

Pancreaticobiliary reflux (PBR) is an important pathologic state that can cause biliary malignancy. PBR can occur regardless of whether the patient has pancreaticobiliary maljunction (PBM) or not. Although it has long been possible to diagnose PBM by various imaging modalities, PBR without PBM has remained difficult to assess. Therefore, the pathological features of PBR without PBM have not been yet fully elucidated. Lately, a new method of diagnosing PBR without PBM has appeared, and the features of PBR without PBM should soon be better understood.

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The common channel is present in 55%-90% of cases [14-16]. The common channel ranges in length from 1 to 12 mm, with a mean length of approximately 4 mm [14,17,18]. In addition to controlling secretion into the duodenum, the sphincter of Oddi also preclude the mixing of bile and pancreatic juice within the duct system. The long common channels with PBM may cause to become the sphincter mechanism impair and induce the reflux of pancreatic juice, as the pressure of the pancreatic duct is higher than that of the bile duct [2].

However, PBR in patients without PBM is being increasingly recognized [2,7-12], and may develop due to a number of reasons: dysfunction of the sphincter of Oddi, periamupullary diverticula, endoscopic sphincterotomy, and endoscopic papillary balloon dilatation. Of these, most cases of PBR without PBM seem to be caused by dysfunction of the sphincter of Oddi [2].

**Etiology of cancer**

Although the etiology of biliary cancer in patients with PBR is not yet fully understood, PBR is believed to play an important role in bile duct carcinoma. Once PBR occurs in the pancreaticobiliary junction, the pancreatic and bile juices become mixed and regurgitated mutually, and stagnate in the gallbladder and the bile duct. As a result, activated pancreatic enzymes induce chronic inflammation of the biliary tree and lead to proliferation of the biliary epithelium; moreover this can even cause the expression of carcinogenic substances in the biliary system [19-22]. Therefore, the carcinogenesis process in cases of biliary cancer with PBR is believed to involve the hyperplasia-dysplasia-carcinoma sequence. Several factors that are reportedly related to carcinogenesis in case of biliary cancer have been identified including p53 mutations, microsatellite instability, Bcl-2, and k-Ras point mutations [22-28].

**Classification**

PBR can be divided into two categories on the presence or absence of PBM. PBM can also be divided into two categories on the presence or absence of common bile duct dilatation (Figure 1).

**PBM with choledochal cysts**

Choledochal cysts are rare congenital biliary tract anomalies formed by biliary tree dilatation. Although the relative frequency of this abnormality in the Western population is 1 in 100000-150000 live births, it is markedly high frequency in Asian countries, particularly Japan, where it may be observed in up to 1 in 1000 [29]. The main clinical symptoms include abdominal pain, vomiting, jaundice, and fever. Although the incidence of cholangitis is unclear, cholangitis was observed as a preoperative symptom in 13.2% of patients [2]. Choledochal cysts are commonly divided into several categories on the anatomical features. In 1959, Alonso-lej et al [30] devised a classification for choledochal cysts that was modified in 1977 by Todani et al [31]. According to Todani’s system, choledochal cysts can be divided into five main types. Nevertheless, in this system, almost all patients with choledochal cysts fall into three categories (Todani’s type I a, I c and IV-A), and are related with PBM.

PBR may contribute to dilatation of the biliary tract.
PBR without choledochal cysts

PBM without a choledochal cyst may result in the reflux of pancreatic juice into the bile duct and may present clinical symptoms similar to those observed in cases with PBM with a choledochal cyst. Cholangitis was observed as a preoperative symptom in 8.9% of patients. However, only few patients with PBM without a choledochal cyst have symptoms in childhood; thus, in these patients, PBM tends to be diagnosed at a later stage than in those with a choledochal cyst. Pancreatic juice is often refluxed into the biliary duct in PBM patients, and this may be associated with a high frequency of biliary cancer among such patients. While both PBM patients with and those without choledochal cysts are at risk for biliary malignancies, they differ in the site of malignancy in the biliary tract.

In a previous study, biliary cancer was noted in 21.6% of adult patients with choledochal cysts, and in 42.2% of patients with PBM without biliary dilatation. Of all cases of biliary cancer associated with PBM without biliary dilatation, 88.1% were cancers of the gallbladder.

PBR without PBM

Lately, several researches on the reflux of pancreatic juice into the bile duct in case without PBM have been published, and the relationship of such a condition with biliary diseases, especially biliary malignancies, is attracting considerable attention. However, these cases do not present specific clinical symptoms and also could not be accurately detected by using current available imaging modalities based on the morphological changes. Thus, it was difficult to predict and detect PBR without PBM. Generally, PBR in these patients is diagnosed on the basis of elevated pancreatic enzyme levels in bile juice samples, or by using magnetic resonance cholangiopancreatography (MRCP) after secretin injection.

Anderson et al. demonstrated that elevated amylase levels in bile juice taken from indwelling T-tubes, suggestive of PBR, were found in 81% (21 of 26) of patients with biliary disease without PBM. Horaguchi et al. presented that elevated amylase levels in bile juice after endoscopic retrograde cholangiopancreatography (ERCP) were found in 26% (46 of 178) of patients with a normal junction. Similarly, Sakamoto et al. detected elevated amylase levels in bile juice in 20% (39 of 196) of patients undergoing cholecystectomy without PBM. Kamisawa et al. focused on the hypothesis that a relatively long common channel without PBM may be related to PBR. They defined a high confluence of the pancreaticobiliary ducts as a common channel length of more than 6 mm, in which communication may be sustained even when the sphincter of Oddi is contracted. They reported that a high confluence of the pancreaticobiliary ducts was found in 1.9% (65 of 3459) of patients who underwent ERCP in their single institute, and that the incidences of gallbladder cancer in patients with a high confluence of the pancreaticobiliary ducts was very high compared to that in controls.

Recently, a multi-center trial in Japan revealed that elevated amylase levels in bile juice after ERCP were found in 5.5% (23 of 420) of patients with a normal junction. This trial showed that the presence of a relative long common channel (not shorter than 5 mm) was the only significant factor for PBR in multivariate analysis, and that the incidence of high amylase levels was significantly higher in patients with gallbladder cancer than in those without gallbladder cancer.

**DIAGNOSIS**

**PBM**

PBM can be detected with ERCP, ultrasonography (US), endoscopic US (EUS), computed tomography and MRCP. ERCP is the gold standard method for diagnosis of PBM, and pancreatography through the minor duodenal papilla can directly demonstrate pancreaticobiliary reflux in PBM patients. When the contrast medium is injected endoscopically through the minor duodenal papilla, it is possible to monitor the reflux of contrast medium into the bile duct through the common channel without outflow into the duodenum. Although ERCP is the diagnostic standard method for PBM, it is somewhat invasive and has a non-negligible risk of morbidity. US can detect choledochal cysts as well as abnormalities of the gallbladder that are possibly associated with PBM. However, because US cannot directly detect PBM, it may...
Endoscopic ultrasound image shows pancreaticobiliary maljunction.

Recently, a new magnetic resonance-based method for diagnosing PBR without PBM has been introduced, and no clinical results have yet been reported (Figure 4). This technique, involving the use of the pancreatic juice as an intrinsic imaging agent, facilitates the examination of pancreatic juice movement similar to more physiological situation. In addition, this technique is not time consuming. Accordingly, the method can be easily adopted as a screening tool for PBR. Therefore, this new technique may reveal what proportion of patients without PBM have PBR, and whether reflux is related to biliary carcinogenesis. Further clinical studies are required.

**THERAPY**

Once PBM is diagnosed, preventive flow-diversion therapy (biloenteric anastomosis and bile duct resection) is executed for patients with choledochal cysts [4,6]. Nevertheless, any treatment for patients with PBM without biliary dilatation and biliary malignancy is controversial. Preventive cholecystectomy is first choice in many institutions because the majority of biliary malignancies that develop in PBM patients without biliary dilatation are cancers of the gallbladder [4,6,47,48]. On the other hand, excision of the extrahepatic bile duct along with the gallbladder is selected by some surgeons [6,49,50]. The treatment for patients with PBR without PBM is not defined because the pathology of PBR without PBM is less well understood. Moreover, strategies for the screening and prevention of PBR without PBM are not yet established.

**CONCLUSION**

PBR is an important pathologic state that can cause biliary malignancy. PBR can occur regardless of the presence of PBM. Although it has been possible to diagnose PBM by using various imaging modalities, PBR without PBM has remained difficult to assess. Thus, the pathological features of PBR without PBM have not yet been fully elucidated. Recently, a new method for diagnosing PBR without PBM has been introduced, and this would enable a better understanding the feature of PBR without PBM.
PBR without PBM.

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