Title: Classification of pancreaticobiliary maljunction and its clinical features in adults

Running title: Classification of pancreaticobiliary maljunction

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Abstract

Background: In pancreaticobiliary maljunction (PBM), reflux of pancreatic juice and bile produces various pathological conditions in the biliary tract and pancreas. Clinical features according to the classification of PBM by confluence between the distal bile duct and the main pancreatic duct proposed in 2015 were evaluated in children.

Methods: Clinical features and complicating diseases according to the PBM classification were evaluated in 168 adult PBM patients. Patency of Santorini duct and associated biliary carcinomas were evaluated in 123 patients.

Results: Similar to children, there were significant differences in age (P<0.01) and type of common bile duct (P<0.01) between the groups of the classification. Unlike in children, there was no significant difference in the incidence of abdominal pain and hyperamylasemia. There were 87 associated biliary carcinomas (79 gallbladder carcinomas and 8 cholangiocarcinomas). PBM patients with a cudgel-type Santorini duct, which is greater than 2 mm in diameter, did not develop biliary carcinomas, compared to 61.1% of those with other types of Santorini duct (P<0.01**).**

Conclusions: Clinical features according to the PBM classification in adults were different from those in children. Although biliary carcinomas were frequently seen in adult PBM patients, none of those with a cudgel-type Santorini duct developed biliary

carcinoma.

Introduction

Pancreaticobiliary maljunction (PBM) is a congenital malformation involving the pancreatic and bile ducts, which usually join anatomically at a location outside the duodenal wall to form a long common channel.[1, 2] The normal location of the sphincter of Oddi, which controls the outflow of pancreatic juice and bile, is usually at the distal end of the bile and pancreatic ducts. In PBM, however, because the common channel is so long that the sphincter cannot directly affect the pancreaticobiliary junction, resulting in reciprocal reflux of pancreatic juice and bile (pancreatobiliary and biliopancreatic reflux), causing a variety of pathological states affecting the pancreas and the biliary tract. There are two types of PBM, with biliary dilatation (congenital biliary dilatation) and without biliary dilatation.[1-5]

Although several classifications of PBM based on the form of the confluence between the distal common bile duct and the main pancreatic duct have been reported,[6-8] there is no widely accepted classification. In 2015, the Committee on Diagnostic Criteria of the Japanese Study Group on Pancreaticobiliary Maljunction proposed a classification of PBM, which divided PBM into four types: (A) stenotic type, (B) non-stenotic type, (C) dilated channel type, and (D) complex type. In Type A, the stenotic or narrow segment of the distal common bile duct joins the common channel, and

dilatation of the common bile duct is seen. In Type B, the distal common bile duct without any stenotic or narrow segment smoothly joins the common channel. In Type C, the narrow segment of the distal common bile duct joins the common channel, and abrupt dilatation of the common channel is seen. Type D involves complicated unions of the pancreaticobiliary ductal systems, such as pancreas divisum, annular pancreas, or other complicated duct systems (Fig 1). In 2017, Urushihara et al. evaluated clinical features according to this classification in children and found that abdominal pain and hyperamylasemia were more frequent in types B and C, and protein plugs were detected in 56.1% of type C.[9] This time, the clinical features, especially the association with biliary carcinoma, were examined according to this classification in adult PBM patients.

In 2005, we examined cholangiopancreatograms of 78 PBM patients and reported that biliary carcinoma was identified significantly less frequently in patients with dorsal pancreatic duct dominance, in which the maximum diameter of the Santorini duct was almost equal to or greater than that of the ventral pancreatic duct. Since the amylase levels in the bile were significantly lower with dorsal pancreatic duct dominance than with a normal pancreatic duct system in PBM patients, we suspected that most pancreatic juice in the upper dorsal pancreatic duct in PBM with dorsal pancreatic duct dominance is drained into the duodenum through the minor duodenal papilla.[10]

Previously, we examined the patency of the Santorini duct by dye-injection endoscopic retrograde pancreatography (ERP). On ERP, contrast medium with indigocarmine was injected into the major duodenal papilla, and the patency of the Santorini duct was determined by observing dye excretion from the minor duodenal papilla in 123 cases. The terminal shape of the Santorini duct showed a relationship to patency. Patency of the Santorini duct was most frequent in cudgel type (87%), followed in descending order of spindle type (82%), stick type (49%), saccular type (27%), branch type (0%), halfway type (0%), and absent (0%) (Fig 2). A stick-type Santorini duct is a gradually narrowing duct (n=63, 51%); a branch-type duct shows gradually narrowing and gives off a few fine terminal ducts (n=15, 12%); a saccular-type duct shows a saccular terminal dilatation (n=15, 12%); spindle-type duct shows ampullary formation (n=11, 9%); cudgel-type duct is greater than 2 mm in diameter (n=8, 7%); and halfway-type shows duct obliteration of the duct near the duodenum (n=7, 6%).[11]

Methods

Between 1975 and October 2018, 185 adult patients (older than 16 years) were diagnosed as having PBM on endoscopic retrograde cholangiopancreatography (ERCP)

at Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital and Toho University Omori Medical Center. The maximum diameters of the common bile duct, common channel, ventral pancreatic duct, and Santorini duct were measured digitally in choledochopancreatograms in and after April 2005, and they were measured using a manual goniometer (Digital Map-meter, Concurve-9, Koizumi Sokki Mfg. Co., Ltd., Tokyo) and corrected for radiological magnification on 50 cholangiopancreatograms before 2005. Clinical features, hyperamylasemia, protein plugs, and associated diseases were evaluated according to the PBM classification.

In 123 cholangiopancreatograms with satisfactory imaging of the pancreatic duct, with filling of at least several pancreatic branch ducts, patency of the Santorini duct was estimated from its terminal shape and observation of contrast medium leak from the minor duodenal papilla on X-ray evaluation. However, since contrast medium leak could not be easily judged on X-ray films in many cases, we focused on the cudgel-type Santorini duct, which is greater than 2 mm in diameter and frequently showed apparent excretion of contrast medium from the minor duodenal papilla. Associated diseases and amylase levels in the bile were compared between PBM patients with cudgel-type and other types of Santorini duct. Cholangiopancreatograms of patients who developed chronic pancreatitis were excluded, as secondary obstruction or dilatation of the

Santorini duct occurs frequently in chronic pancreatitis.

PBM patients were divided into those with and without biliary dilatation. Measurement of the diameter of the bile duct is recommended using imaging modalities that do not increase pressure in the biliary system, such as ultrasonography and magnetic resonance cholangiopancreatography (MRCP), since endoscopic retrograde chorangiography (ERC) may not show the true diameter of the bile duct because of the injection of contrast medium into the bile duct, leading to dilatation of the common bile duct.[3, 4] Although standard values for the maximum diameter of the common bile duct at each age have been presented using ultrasonography,[3] there are no data for ERC. In the present study, PBM without biliary dilatation was diagnosed when the maximum diameter of the common bile duct was less than 10 mm, and the shape of the common bile duct seemed to be almost normal.

The χ^2 test and Fisher's exact test were used to analyze categorical data. The Kruskal-Wallis test and the Mann-Whitney *U*-test were used to compare continuous data. A *P*-value of less than 0.05 was considered significant. All statistical analyses were performed with EZR version 1.37, a graphical user interface for R software (The R Foundation for Statistical Computing, version 3.4.1).

This study was approved by the institutional review board of Tokyo Metropolitan

Cancer and Infectious Diseases Center Komagome Hospital (No. 2219) and the ethics committee of Toho University Omori Medical Center (No. M18257).

Results

PBM classification and clinical features

Seventeen patients whose cholangiopancreatograms of the pancreaticobiliary junction were unclear were excluded, leaving 168 patients included in this study. Cholangiopancreatograms of the 168 PBM patients were divided into four groups according to the PBM classification (Table 1): type A in 55 patients (32.7%), type B in 96 patients (57.1%), type C in 11 patients (6.5%), and type D in 6 patients (3.6%). PBM patients with type D had complete pancreas divisum (n=3) and incomplete pancreas divisum with a very short ventral pancreatic duct (n=3).

There were significant differences in age ($P<0.01$) and type of common bile duct ($P<0.01$) between the groups. Patients with type A were younger and had a higher incidence of congenital biliary dilatation (94.5%). PBM without biliary dilatation was frequently seen in patients with type B (92.7%) (Table 2).

Abdominal pain and hyperamylasemia were detected in 48.2% (81/168) and 22.4% (33/147) of adult patients with PBM, and there was no significant difference in their

incidences among PBM types. Jaundice as the clinical finding in adults with PBM was frequently seen in patients with type B (20.8%), whereas acute pancreatitis was seen in patients with type A (10.9%) and type B (5.2%). Protein plugs were detected in no patients (Table 2).

There were 87 associated biliary carcinomas: 79 gallbladder carcinomas and 8 cholangiocarcinomas. Gallbladder carcinoma was present in 67.7% of type B PBM patients, significantly more frequently than in other types ($P<0.01$) (Table 3).

Cudgel-type Santorini duct and associated biliary carcinoma

The terminal shapes of the Santorini duct on cholangiopancreatograms of 123 PBM patients were stick type (n=40, 32.5%), branch type (n=15, 12.2%), cudgel type (n=10, 8.1%), saccular type (n=3, 2.4%), halfway type (n=24, 19.5%), and absent (n=31, 25.2%). Patency of a cudgel-type Santorini duct was confirmed by pancreatography via the minor papilla in 3 patients and was evaluated on X-ray films in the other patients (Fig 3).

A cudgel-type Santorini duct was seen frequently in congenital biliary dilatation ($P<0.05$). No associated biliary carcinoma was seen in PBM patients with the cudgel-type, compared to 61.1% of those with other types of Santorini duct ($P<0.01$). Mean

amylase levels in the bile of PBM patients with the Cudgel-type and other-type Santorini duct were 82786 U/L and 123699 U/L respectively, but the difference was not significant (Table 4).

Discussion

Clinical features were evaluated according to the classification of PBM in adults. The types were different compared to those in children as reported by Urushihara et al. In their study,[9] dilatation of the common bile duct was observed in 92.4%, and the frequencies of types A, B, and C were 41.3%, 23.9%, and 30.9%, respectively. However, in the present study, types A, B, and C were seen in 32.7%, 57.1%, and 6.5%, respectively, and the common bile duct was not dilated in 55.9%. Similar to children, patients with type A were younger, had a higher incidence of congenital biliary dilatation, and PBM without biliary dilatation was frequent in type B. However, incidences of abdominal pain (48.2% vs. 75.3%[9]) and hyperamylasemia (22.4% vs. 61.1%[9]) were less frequent in adults compared to those in children, and there was no significant difference in their incidences among PBM types. In congenital biliary dilatation in children, protein plugs are frequently formed in the dilated common channel. Plugs are compacted in the common channel or the narrow segment, which

increase pancreatobiliary ductal pressure, causing symptoms such as abdominal pain due to acute pancreatitis or cholangitis.[12] Although protein plugs were detected in 36.9% of children with PBM[9], no patients had protein plugs in the present study. In particular, incidence of type C in which abdominal pain (85.7%[9]), hyperamylasemia (72.5%[9]) and protein plugs (56.1%[9]) were frequently detected in children, was lower in adults (6.5%) compared to 30.9%[9] in children.These findings seem to be caused by the fact that many patients with congenital biliary dilatation with clinical symptoms such as abdominal pain have been diagnosed and operated during childhood. On the other hand, few patients with PBM without biliary dilatation have symptoms in childhood, and they are usually not diagnosed until adulthood. Furthermore, many of them are diagnosed in association with advanced-stage gallbladder carcinoma, which carries a poor prognosis.[1, 5, 13]

Another marked difference was frequent association with biliary carcinoma in adult patients with PBM. In the present study, 87 (51.8%) of 168 patients with PBM had associated biliary carcinoma, with 47.0% having gallbladder carcinoma and 4.8% having cholangiocarcinoma. A nationwide survey in Japan (n=2561) reported biliary carcinomas in 21.6% of adult patients with congenital biliary dilatation and 42.4% of PBM patients without biliary dilatation.[14] In adult patients with PBM and biliary

carcinomas, cholangiocarcinoma and gallbladder carcinoma were seen in 32.1% and 62.3%, respectively, of cases with congenital biliary dilatation and in 7.3% and 88.1%, respectively, of PBM patients without biliary dilatation. In pediatric patients, biliary carcinoma was seen in only one patient with congenital biliary dilatation.[14] Since the action of the sphincter of Oddi in PBM does not directly affect the pancreaticobiliary junction, both pancreatic juice and bile reflux. Since the pancreatic duct usually has higher hydropressure than the bile duct, in PBM there is frequent reflux of pancreatic juice into the biliary tract, which intermingles with the bile and persists in the biliary tract. This results in activation of pancreatic enzymes, which then attack biliary tract epithelial cells along with increased secondary bile acids and other mutagens. These actions result in hyperplastic change with increased cell proliferation. Then, biliary tract carcinogenesis occurs as a result of oncogene and/or tumor suppressor gene mutations in the epithelia.[15-17] Since carcinogenesis in PBM patients is strongly related to long-term stagnation of bile mixed with pancreatic juice, most of biliary carcinomas associated with PBM without biliary dilatation in which abnormal stagnation of bile in the common bile duct rarely occurs, are gallbladder carcinomas. Biliary carcinogenesis in PBM patients is thought to involve the hyperplasia-dysplasia-carcinoma sequence caused by chronic inflammation resulting from pancreatobiliary reflux.[1,17] Tokiwa et al.

reported finding gallbladder epithelial hyperplasia in 50% of 28 pediatric patients with PBM;[18] however, the incidence of high-grade hyperplasia increases with age, and dysplasia or metaplasia of the gallbladder epithelium is typically detected only from adolescence onwards.[19,20]

In the embryo, the Santorini duct is the main drainage duct of the dorsal pancreatic primordium. After the dorsal pancreatic duct and ventral pancreatic duct join, the ventral pancreatic duct becomes the dominant duct, with the dorsal pancreatic duct atrophying to a certain degree at its duodenal end and becoming a smaller duct.[21,22] Only 41% of normal control cases showed patency of the Santorini duct in a previous study using dye-injection ERP, with cases showing adequate excretion of pancreatic juice from the minor duodenal papilla being quite rare.[11] The caliber of a patent Santorini duct was larger than that of a non-patent Santorini duct, and a Santorini duct with a large caliber sometimes showed large excretion of pancreatic juice.[23] Therefore, the focus was on the cudgel-type Santorini duct in the present study. A cudgel-type Santorini duct was found in 10 patients, and none of them had biliary carcinoma. Meanwhile, biliary carcinomas were seen in 69 (61.1%) PBM patients with other types of Santorini duct. Although a significant difference was not apparent, mean amylase level in the bile of PBM patients was lower with a cudgel-type Santorini duct than with other types of Santorini duct.

This might be due to the small number of PBM patients with a cudgel-type Santorini duct in which amylase levels in the bile were examined. It might be that, in PBM with a cudgel-type Santorini duct, the pancreatic juice in the upper pancreatic dorsal duct drains mostly into the duodenum through the minor duodenal papilla, with less reflux of pancreatic juice into the biliary tract, which decreases the frequency of biliary carcinogenesis.

Recently, diagnostic pancreatography has been avoided to prevent post-ERCP pancreatitis in many cases. Although direct cholangiopancreatography is necessary in many PBM cases, ERCP is avoided in typical cases of PBM that can be diagnosed only by MRCP, since excessive contrast medium can easily be injected into the main pancreatic duct through the long common channel. A cudgel-type Santorini duct could also be detected on MRCP in 4 of 5 patients. On MRCP, PBM patients with a large Santorini duct might develop biliary carcinoma less frequently. Bile duct resection and bilioenteric anastomosis that blocks the reciprocal reflux of bile and pancreatic juice are standard surgical procedures for congenital biliary dilatation[1,4,5], but close follow-up may be one of the selected options in patients with a cudgel-type Santorini duct and several risk factors for operation. An endoscopic approach that dilates the Santorini duct and changes the flow of the pancreatic juice may become one of the management

choices in PBM patients with a high risk for surgery in the future.

This study had several limitations. First, it was conducted retrospectively during a long period of 43 years in two institutions. Methods and systems of ERCP were different in each institute and changed with time. Second, the number of cases in which amylase levels in the bile were examined was small in PBM patients with a cudgel-type Santorini duct.

In conclusion, clinical features according to the PBM classification were different in adults from those in children. In adults, there was no relationship to abdominal pain or hyperamylasemia, but type B frequently developed gallbladder carcinoma. No biliary carcinoma developed in PBM patients with a cudgel-type Santorini duct. A patent Santorini duct might prevent biliary carcinogenesis in PBM.

All authors have no conflict of interest. No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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Figure legends

Figure 1 Classification of pancreaticobiliary maljunction proposed in 2015 (referred from Ref 9).

Figure 2 Pancreatograms showing the classification of the terminal shape of the Santorini duct.

Figure 3 Pancreatogram of congenital biliary dilatation with a cudgel-type Santorini duct.

(A) stenotic type (B) non-stenotic type (C) dilated channel type (D) complex type

Fig.1

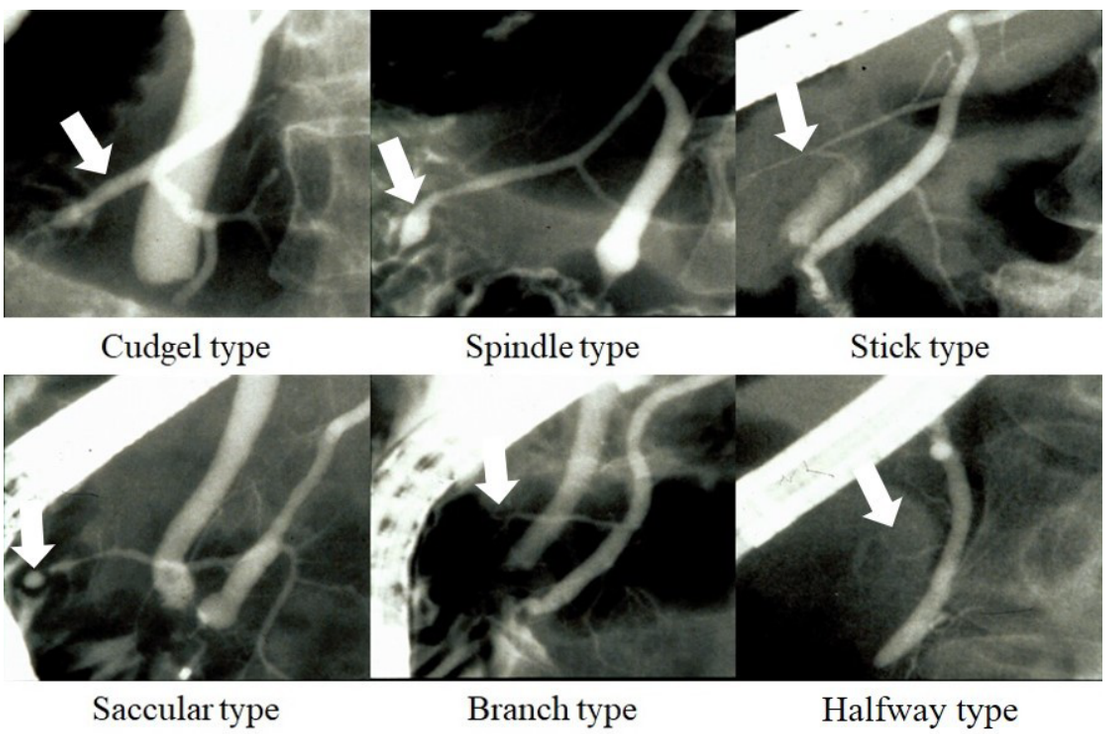

Fig2

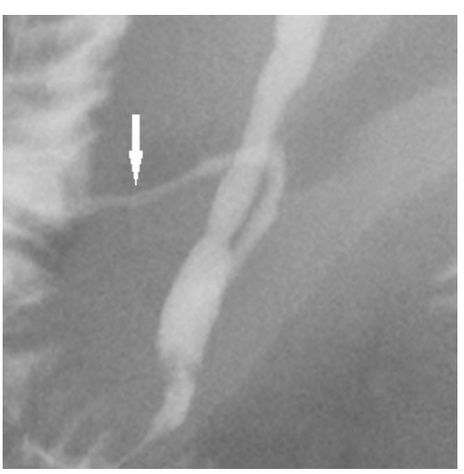

Fig.3

Table 1 Demographic characteristics of adult patients with pancreaticobiliary maljunction

	n=168
Male	40 (23.8%)
Age (years*)	56.4±14.8
PBM classification	
Type A, stenotic type	55 (32.7%)
Type B, non-stenotic type	96 (57.1%)
Type C, dilated channel type	11 (6.5%)
Type D, complex type	6 (3.6%)

PBM: pancreaticobiliary maljunction

* mean±SD

Table 2 Characteristics of the four types of pancreaticobiliary maljunction in adult patients

	A (n=55)	B (n=96)	C (n=11)	D (n=6)	*P*-value
Male	14 (25.5%)	21 (21.9%)	4 (36.4%)	1 (16.7%)	0.72
Age (years*)	49.9±16.8	60.0±12.4	57.9±14.5	56.3±13.6	<0.01
Type of common bile duct					
Congenital biliary dilatation	52 (94.5%)	7 (7.3%)	9 (81.8%)	4 (66.7%)	<0.01
PBM without biliary dilatation	1 (1.8%)	89 (92.7%)	2 (18.2%)	2 (33.3%)	<0.01
Unknown	2 (3.6%)	0	0	0	
Maximum diameter of the common bile duct (mm*)	27.2±13.0	8.4±3.4	21.9±12.9	27.4±19.9	<0.01
Length of the common channel (mm*)	18.7±8.8	20.2±7.6	24.3±9.3	21.2±11.5	0.21
Maximum diameter of the ventral pancreatic duct (mm*)	2.7±1.4	2.5±0.9	2.8±0.9	2.7±1.1	0.85
Serum amylase levels (U/L*)	127.3±134.0	124.4±170.1	200.4±204.2	81.3±31.3	0.45
Hyperamylasemia	13/52 (25.0%)	16/79 (20.3%)	4/10 (40.0%)	0/6 (0%)	0.29
Clinical findings					
Abdominal pain	32 (58.2%)	41 (42.7%)	5 (45.5%)	3 (50.0%)	0.31
Back pain	1 (1.8%)	3 (3.1%)	0	0	1
Jaundice	0	20 (20.8%)	1 (9.1%)	1 (16.7%)	<0.01
Association with acute pancreatitis	6 (10.9%)	5 (5.2%)	0	0	0.48

PBM: pancreaticobiliary maljunction

* mean±SD

Table 3 Associated biliary carcinoma in the four types of pancreaticobiliary maljunction in adult patients

	A (n=55)	B (n=96)	C (n=11)	D (n=6)	*P*-value
Associated biliary carcinoma					
Gallbladder carcinoma	10 (18.2%)	65 (67.7%)	2 (18.2%)	2 (33.3%)	<0.01
Cholangiocarcinoma	3 (5.5%)	5 (5.2%)	0	0	1

Table 4 Characteristics of PBM patients with cudgel-type and other-type Santorini duct

	Cudgel type (n=10)	Other types (n=113)	*P*-value
Male	4 (40.0%)	26 (23.0%)	0.26
Age (years*)	45.0±14.6	57.2±14.3	<0.05
Type of common bile duct			
Congenital biliary dilatation	8 (80.0%)	43 (38.0%)	<0.05
PBM without biliary dilatation	2 (20.0%)	69 (61.1%)	<0.05
Unknown	0	1 (0.9%)	
Maximum diameter of the ventral pancreatic duct (mm*)	2.7±1.8	2.5±0.9	0.47
Maximum diameter of Santorini duct (mm*)	2.6±0.8	1.3±0.6	<0.01
Associated biliary carcinoma	0	69 (61.1%)	<0.01
Gallbladder carcinoma	0	62 (54.9%)	<0.01
Cholangiocarcinoma	0	7 (6.2%)	1
Amylase level in the bile (U/L*)	82786±70766 (n=7)	123699±160136 (n=49)	0.51

PBM: pancreaticobiliary maljunction

* mean±SD