The process of diagnosing pancreaticobiliary maljunction

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ABSTRACT

Background: Pancreaticobiliary maljunction (PBM) patients have a high rate of biliary cancers. This study aimed to show strategy for early detection of PBM before the development of biliary cancer.

Methods: We investigated pancreatobiliary complications, age at diagnosis and process of diagnosis in 111 PBM patients (with biliary dilatation (BD) (n=55) and without BD (n=56)).

Results: Eighteen patients of 55 PBM patients with BD (33%: bile duct cancer, n=9; gallbladder cancer, n=10) and 33 of 56 PBM patients without BD (68%: gallbladder cancer only) developed biliary cancer. PBM patients with BD in association with gallbladder cancer were older than those without gallbladder cancer ($p<0.01$). The number of PBM patients with associated biliary cancer increased with age ($p<0.01$). Thirteen PBM patients with BD and 33 PBM patients without BD were diagnosed by symptoms due to advanced biliary cancers. PBM without BD was suspected in 9 patients based on findings of gallbladder wall thickening on ultrasonography (US), and the diagnosis was made with magnetic resonance cholangiopancreatography (MRCP) and/or endoscopic retrograde cholangiopancreatography before the development of biliary cancer.

Conclusions: For early detection of PBM without BD, MRCP should be performed for individuals showing gallbladder wall thickening on US, even in the absence of symptoms.

Key words: pancreaticobiliary maljunction; congenital biliary dilatation; gallbladder cancer; bile duct cancer, ultrasonography

INTRODUCTION

Pancreaticobiliary maljunction (PBM) is a congenital anomaly defined as a junction of the pancreatic and bile ducts located outside the duodenal wall, and usually forming a markedly long common channel (1-3). As the action of the sphincter of Oddi does not have a functional impact on the junction of the pancreatic and bile ducts in PBM patients, PBM causes continuous reciprocal reflux of pancreatic juice and bile. This results in various pathological conditions of the biliary tract and pancreas. Hydropressure is usually greater in the pancreatic

duct than in the bile duct, and pancreatic juice frequently flows back into the biliary duct (pancreatobiliary reflux), representing a high risk factor for biliary cancer. Bile sometimes refluxes into the pancreatic duct in some situations (biliopancreatic reflux), inducing pancreatitis (1-3).

PBM is divided into PBM with biliary dilatation (BD) (congenital biliary dilatation) and PBM without BD. Onset in many patients with PBM with BD involves abdominal pain, vomiting or jaundice due to cholangitis and pancreatitis during the neonatal period, infancy or early childhood, and surgical treatment is provided. However, many PBM patients with BD who do not have clinical symptoms are left untreated in childhood and cancerous changes can then occur in adolescence or adulthood. On the other hand, few PBM patients without BD experienced symptoms in childhood and the condition is usually not diagnosed until adulthood. Furthermore, many patients with PBM without BD are diagnosed with advanced-stage gallbladder cancer, which carries a poor prognosis (2,3). Strategies are needed to diagnose PBM with or without BD before biliary cancer occurs. The present study investigated clinical differences among age groups and the process for diagnosis of PBM with and without BD.

METHODS

Study patients

Between 1978 and 2013, a total of 111 patients were diagnosed as having PBM in Tokyo Metropolitan Komagome Hospital. A long common channel was confirmed on imaging studies such as endoscopic retrograde cholangiography (ERCP, n=107), transhepatic cholangiography (n=3), intraoperative cholangiography (n=3), or magnetic resonance cholangiopancreatography (MRCP, n=58); and/or by pathological studies of resected (n=3) or autopsied (n=16) specimens. Of these, patients in whom maximal diameter of the bile duct was ≤ 10 mm were diagnosed with PBM without BD. When the bile duct was involved with associated gallbladder cancer, diameter of the intact distal portion of the bile duct was measured.

Of these, 55 patients (14men, 51women) were diagnosed with PBM with BD, and 56 patients (12 men, 44 women) were diagnosed with PBM without BD. Patients were divided into four groups according to the age at initial diagnosis: ≤ 39 years; 40-49 years; 50-59 years; and ≥ 60 years).

Tumor stage of bile duct and gallbladder cancer was judged according to the general rules for Surgical and Pathological Studies on Cancer of the Biliary Tract (4).

This study was approved by institutional review board of Tokyo Metropolitan Komagome Hospital.

Data analysis

We investigated the differences in clinical features including complications according to the age at which PBM was initially diagnosed, and the process of the diagnosis.

Statistical analysis was performed using chi-squared analysis or Mann-Whitney's U test. The relationship between the risk of biliary cancer and age was assessed using logistic regression analysis. Values of $p < 0.01$ were considered statistically significant.

RESULTS

Pancreatobiliary complications

Eighteen of 55 PBM patients (33%) with BD had biliary cancers (gallbladder cancer, n=10; bile duct cancer, n=9). Bile duct cancers occurred in all 3 patients who underwent initially cystenterostomy as an infant. One patient showed both bile duct cancer (dominant) and gallbladder cancer simultaneously. One patient had multiple bile duct cancers. In 1 patient, bile duct cancer occurred metachronously after resection of the first bile duct cancer. Acute pancreatitis, chronic pancreatitis and biliary stones were associated in 4, 3 and 13 patients, respectively.

Thirty-eight patients of 56 PBM patients (68%) without BD had biliary cancers (only gallbladder cancer, n=38). Acute pancreatitis, chronic pancreatitis and biliary stones were associated in 4, 1 and 10 patients, respectively (table 1).

Age at diagnosis

Median age at initial diagnosis was significantly lower in PBM patients with BD than that in PBM without BD (48.0 years (quartile range: 27.0-63.0 years) vs. 58.0 years (49.2-67.0 years); $p < 0.01$). Eleven PBM patients with BD showed episodes of repeated abdominal pain in a child, including 2 patients misdiagnosed with autotoxemia due to periodicity nausea and vomiting needing hospitalization in a child.

No significant difference in median age at diagnosis was apparent between PBM patients with BD in association with bile duct cancer (58.5 years (36.5-64.5 years)) and without bile duct cancer (48.5 years (30.7-63.2 years)). However, median age was higher in PBM patients with BD in association with gallbladder cancer (68.5 years (49.5-76.5 years)) than in those without gallbladder cancer (40.0 years (23.5-57.5 years), $p < 0.01$). No significant difference in median age at diagnosis was

Table 1 - Pancreatobiliary diseases associated with PBM with and without biliary dilatation

Initial symptoms	PBM with biliary dilatation		PBM without biliary dilatation	
	Biliary cancer (+) (n=18)	Biliary cancer (-) (n=37)	Biliary cancer (+) (n=38)	Biliary cancer (-) (n=18)
Bile duct cancer	9*	0	0	0
Gallbladder cancer	10**	0	38	0
Acute pancreatitis	0	4	3	1
Chronic pancreatitis	0	3	0	1
Biliary stones	3	10	4	6

*Three bile duct cancers occurred after initial operation of cystenterostomy.

**Double bile duct and gallbladder cancers occurred in 1 patient.

Table 2 - Comparison of age of PBM patients with and without biliary dilatation in association with gallbladder cancer

	Gallbladder cancer (+)	Gallbladder cancer (-)	p value
PBM with biliary dilatation years, median (quartile range)	68.5* (49.5-76.5)	40.0 (23.5-57.5)	<0.01
PBM without biliary dilatation years, median (quartile range)	58.5* (54.0-63.5)	54.0 (41.5-62.5)	0.28

*p=0.14 between PBM with and without biliary dilatation

Table 3 - Relationship between age at diagnosis and associated biliary cancer in PBM with and without biliary dilatation

PBM with biliary dilatation (n=55)				PBM without biliary dilatation (n=56)	
Age (years)	n	Bile duct cancer (n=6*)	Gallbladder cancer (n=9)	n	Gallbladder cancer (n=38)
<39	21	1 (5%)	0 (0%)	3	0 (0%)
40-49	8	1 (13%)	2 (25%)	11	6 (55%)
50-59	8	1 (13%)	1 (13%)	18	14 (78%)
60-	17	3 (18%)	6 (35%)	24	18 (75%)

*Except bile duct cancers developed after initial operation of cystenterostomy.

seen between PBM patients without BD in association with gallbladder cancer (58.5 years (54.0-63.5 years)) and without gallbladder cancer (54.0 years (41.5-62.5 years)) (table 2).

The number of PBM patients associated with biliary cancer increased with age ($p<0.01$). PBM patients with BD ≥ 60 years old and PBM patients without BD ≥ 40 years old had frequently associated biliary cancers. In PBM patients ≤ 39 years old, only 1 patient with BD developed bile duct cancer after cystoduodenostomy (table 3).

Initial symptoms and diagnostic process for PBM

Major initial symptoms in PBM patients were abdominal pain and obstructive jaundice in almost all ages (figure 1).

PBM with BD and biliary cancer were diagnosed in 13 patients after examination of abdominal pain,

obstructive jaundice, fever and weight loss induced by associated biliary cancer. PBM with BD and biliary cancer were diagnosed in 2 asymptomatic patients after examination for BD detected by screening ultrasonography (US). Stages of biliary cancer in the former 13 patients were stage I in 1 and stage IV in 12, and surgical resection was performed in 5 patients. Stages of biliary cancer in the latter 2 asymptomatic patients were stage I in 1 and stage II in 1, with curative resection performed in each case. Major symptoms in the 40 PBM patients with BD who were diagnosed without biliary cancer were abdominal pain and obstructive jaundice induced by PBM itself or associated diseases such as biliary stones, and acute or chronic pancreatitis. PBM was diagnosed in 6 asymptomatic patients after examination for BD detected by screening US. Flow-diversion surgery including cholecystectomy, bile duct resection and bilioenteric anastomosis was performed in 34 patients.

Figure 1 - Initial symptoms in PBM patients with and without biliary dilatation among age groups

PBM without BD and with biliary cancer were diagnosed in 33 patients after examination of abdominal pain, obstructive jaundice, and other symptoms induced by associated biliary cancer. PBM without BD and with biliary cancer were diagnosed in 5 asymptomatic patients after examination for gallbladder tumor detected by screening tests such as US. Stages of biliary cancer in the former 33 patients were stage I in 1, stage II in 1 and stage IV in 31, and surgical resection was performed in 5 patients. Stages of biliary cancer in the latter 5 asymptomatic patients were stage I in 2, stage II in 2 and stage III in 1, with curative resection performed in each case. Major symptoms in PBM patients without BD who were diagnosed without biliary cancer were

abdominal pain and obstructive jaundice induced by associated diseases such as biliary stones, and other malignancies (table 4).

PBM without BD was suspected in 9 patients, including 6 asymptomatic patients, based on thickening of the gallbladder wall on US, and the diagnosis was made after examination (computed tomography (n=9), magnetic resonance cholangiopancreatography (MRCP) (n=5), endoscopic ultrasonography (n=5), and endoscopic retrograde cholangiopancreatography (ERCP) (n=9). Under the diagnosis of PBM without BD, all 9 patients underwent prophylactic cholecystectomy, and amylase levels in the bile duct were markedly elevated. Histological findings of the resected gallbladder were

Table 4 - Initial symptoms of PBM patients with and without biliary dilatation

Initial symptoms	PBM with biliary dilatation		PBM without biliary dilatation	
	Biliary cancer (+) (n=15)	Biliary cancer (-) (n=40)	Biliary cancer (+) (n=38)	Biliary cancer (-) (n=18)
Abdominal pain	4	21 PBM 11 Biliary stone 5 Acute pancreatitis 3 Chronic pancreatitis 2	16	7 Pancreatic cancer 2 Biliary stone 3 Acute pancreatitis 1
Obstructive jaundice	7	4 Biliary stone 3 Chronic pancreatitis 1	13	2 Liver cancer 1 Biliary stone 1
Fever	1	1	1	0
Others	1	0	3	3
Asymptomatic	2	6	5	6
Unknown	0	8	0	0

Table 5 - PBM without biliary dilatation diagnosed based on gallbladder wall thickening on ultrasonography

Case	Age	Abdominal pain	Gallbladder wall thickening on ultrasonography	Pathological findings of the gallbladder
1	30	-	+	hyperplasia
2	65	+	+	hyperplasia
3	41	-	+	hyperplasia
4	70	-	+	hyperplasia
5	42	+	+	hyperplasia, chronic cholecystitis
6	47	+	+	hyperplasia, chronic cholecystitis
7	36	-	+	hyperplasia, chronic cholecystitis
8	54	-	+	hyperplasia, adenomyomatosis
9	73	-	+	hyperplasia, adenomyomatosis

epithelial hyperplasia (n=9), chronic cholecystitis (n=3) and adenomyomatosis (n=2). Bile duct cancer has not occurred in any patients during follow up (*table 5*).

DISCUSSION

PBM patients show a high rate of biliary cancers. According to a nationwide survey in Japan (5), biliary cancer occurred in 21.6% of adult patients with PBM with BD and 42.2% of adult patients with PBM without BD. In patients with biliary cancers in association with PBM, the frequencies of bile duct cancer and gallbladder cancer were 32.1% and 62.3% in PBM patients with BD, and 7.3% and 88.1% in PBM patients without BD, respectively. In the present series, bile duct cancer and gallbladder cancer occurred in 16% and 18% of PBM patients with BD, respectively, and gallbladder cancer occurred in 68% of PBM patients without BD. The higher frequency of gallbladder cancer in association with PBM without BD might be due to the fact that our hospital is a tertiary referred hospital of cancer patients. In the survey (5), PBM patients with biliary cancer were approximately 10 years older than patients without biliary cancer. In the present series, PBM patients with BD in association with gallbladder cancer were more than 20 years older than those without gallbladder cancer.

Many PBM patients with BD are diagnosed with abdominal pain, vomiting or jaundice due to cholangitis and pancreatitis during the neonatal stage, infancy or early childhood, and are treated with flow-diversion surgery (3,5). PBM patients with BD who have mild or no symptoms are left untreated in childhood. Most are diagnosed in adulthood with the finding of BD on US, but around 24 % are diagnosed after examination of symptoms induced by associated advanced biliary cancer that could not be curatively resected. Of note was the finding that 11 PBM patients with BD in this

series had experienced repeated episode of abdominal pain as a child, including 2 patients misdiagnosed with autotoxemia.

On the other hand, PBM patients without BD rarely show symptoms due to the maljunction, and most are diagnosed in association with advanced-stage gallbladder cancer. In the present series, 58% of PBM patients without BD were diagnosed with symptoms induced by the associated advanced gallbladder cancer, and 82% were stage IV at diagnosis.

Epithelial hyperplasia of the gallbladder is induced by long-standing continuous stasis of the bile intermingled with refluxed pancreatic juice, resulting in thickening of the gallbladder wall in PBM patients (2,3,6-8). We have prospectively checked for PBM after identifying gallbladder wall thickening on US since 1995. Nine PBM patients without BD were diagnosed after examination of the biliary tree under suspicion of PBM based on gallbladder wall thickening on US. All patients underwent prophylactic cholecystectomy, and remained well during the follow-up period. Amylase levels in the bile duct were markedly elevated and histological examination of the resected gallbladder showed epithelial hyperplasia. ERCP is a gold standard for the diagnosis of PBM, but is an invasive method that can cause adverse effects such as pancreatitis. Currently, MRCP has replaced ERCP in the diagnosis of many pancreatobiliary diseases, but atypical PBM cases with a relatively short common channel should be confirmed by ERCP (9). To detect PBM without BD before the development of gallbladder cancer, performing MRCP is important for patients showing gallbladder wall thickening on screening US under suspicion of PBM without BD.

The number of PBM patients with associated biliary cancer increased with age. According to a report by Aoki et al., biliary cancer occurred in 0 of 59 PBM junior patients (0-14 years), 9% of 22 PBM adolescent patients

(15-39 years) and 53% of 38 senior PBM patients (40-75 years), and the histological incidence of metaplasia of the gallbladder among PBM patients increased with age (11% of adolescents vs. 42% of senior patients) (6). Sugai et al. also reported that the incidence of chronic inflammation, hyperplasia and metaplasia of gallbladder was lower in children than in adults (7). These results suggest that gallbladder cancer occurs in PBM patients as a result of repeated destruction and regeneration of the gallbladder epithelium due to prolonged reflux of pancreatic juice (hyperplasia-dysplasia-carcinoma sequence).

A major limitation of the present investigation was the retrospective nature of the study spanning 35 years, particularly since diagnostic modalities have varied substantially at different periods. However, the present study included a large number of PBM patients from a single center. Another limitation was that we have seen only adult PBM patients.

CONCLUSION

In conclusion, PBM with BD may exist behind repeated episode of unexplained abdominal pain as a child. To detect PBM without BD before the development of gallbladder cancer, MRCP should be performed

for individuals showing gallbladder wall thickening on US, even if the patients are asymptomatic.

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