J Gastroenterol 2005; 40:396–401
DOI 10.1007/s00535-005-1554-7

Journal of Gastroenterology

Clinical study of choledochocele: is it a risk factor for biliary malignancies?

Jun Horaguchi, Naotaka Fujita, Go Kobayashi, Yutaka Noda, Kei Ito, and Osamu Takasawa

Department of Gastroenterology, Sendai City Medical Center, 5-22-1 Tsurugaya, Miyagino-ku, Sendai 983-0824, Japan

Background. We aimed to clarify the clinical characteristics of choledochocele and to evaluate the possibility of choledochocele as a risk factor for biliary malignancies. ***Methods.*** The clinical feature, the configuration of the pancreatobiliary ductal system, coexistent pancreatobiliary lesions, and amylase level in bile in 21 patients with choledochocele were reviewed. The correlation between the configuration, comorbid diseases, and amylase level in the bile was investigated. ***Results.*** There was a female predominance, and 57% of the patients showed abdominal pain. Quite a few patients showed elevation of the levels of hepatobiliary enzymes. The configuration of the pancreatobiliary ductal system and choledochocele was classified into two categories: type I, where the choledochocele and pancreatic duct were visualized independently or simultaneously (90.5%); and type II, where the pancreatic duct was visualized after filling of the choledochocele (9.5%). Among coexistent biliopancreatic diseases, biliary stone diseases were the most frequent. Biliary malignancy was seen in 3 patients (14.3%). The amylase level in the bile was high in 50% (4/8) of the patients examined. The rate of abnormal elevation of amylase level in the bile in the two types of pancreatobiliary ductal system and choledochocele was 3/7 and 1/1, respectively. ***Conclusions.*** The prevalence of organic abnormal arrangement of the pancreatobiliary ductal system in which the choledochocele serves as a common channel is low. However, there are patients with suspected functional abnormal arrangement of the pancreatobiliary ductal system, who may possibly be a high-risk group for biliary malignancy.

Received: June 7, 2004 / Accepted: January 14, 2005
Reprint requests to: J. Horaguchi

Key words: choledochocele, biliary malignancy, abnormal arrangement of the pancreatobiliary ductal system, congenital choledochal cyst

Introduction

Choledochocele is a relatively rare anomaly, classified as Alonso-Lej's[1] type III, seen in about 1.5% of congenital choledochal cysts.[2] Different from Alonso-Lej's type I congenital choledochal cyst, this anomaly is not generally regarded as being associated with abnormal arrangement of the pancreatobiliary ductal system or biliary malignancy. Recently, there have been some reports of patients with choledochocele associated with biliary malignancy,[3,4] as well such patients with high levels of amylase in bile.[5–7] The possibility of choledochocele as a high-risk state for biliary malignancy is gaining interest. We reviewed patients with choledochocele to clarify its clinical features; we classified the configuration of the choledochocele and the pancreatobiliary ductal system, and evaluated the risk of choledochocele causing reflux of pancreatic juice into the bile duct, which may be followed by development of biliary malignancies.

Methods

Twenty-one patients in our department, who were diagnosed by endoscopic retrograde cholangiopancreatography (ERCP) as having choledochocele, between January 1985 and August 2003, were included in this study. The diagnosis of choledochocele was made when: (1) there was endoscopically obvious cystic bulging of the oral protrusion of the papilla of Vater and (2) cystic dilatation of the common channel or of the bile duct terminal distal to the point where

the duct penetrates the muscularis propria of the duodenum.

The four features below were evaluated.

Clinical features of choledochocele

The prevalence of choledochocele among patients who underwent ERCP, age at the time of diagnosis, sex, clinical symptoms, laboratory data, and the sizes of the choledochocele and the bile duct were reviewed. The sizes of the choledochocele and the bile duct were measured on X-ray films taken during ERCP. The size of the choledochocele was determined on the X-ray film showing the maximum size in each patient.

Configuration of the pancreatobiliary ductal system in choledochocele

Even with the compression method, it is not possible to evaluate the configuration of the choledochocele and the pancreatic duct by using spot films after the filling of the ducts by contrast. We therefore carried out serial recordings of the visualization of the structures from the commencement of contrast medium injection to completion of the visualization of those structures on the X-ray film. Classification of the configuration of the choledochocele and pancreatic duct terminal was attempted by interpreting film images obtained serially during the injection of the contrast at ERCP.

Comorbid pancreatobiliary diseases in patients with choledochocele

Comorbid diseases of the pancreatobiliary system were investigated in the 21 patients.

Amylase level in bile in patients with choledochocele

The level of amylase in the bile was measured in eight patients to evaluate whether pancreatic juice was refluxed into the bile duct. Bile was collected via a catheter cannulated into the bile duct through the papilla of Vater during ERCP in five patients and intraoperatively in three patients. The level of amylase in the bile was regarded as being high when it was greater than the normal upper limit of the serum amylase level (168 IU/l). Correlations between amylase level and comorbid diseases, the type of configuration of the choledochocele and pancreatobiliary ductal system, and the size of the choledochocele and the bile duct were investigated.

Results

Clinical features of choledochocele

During the period previously mentioned, 7918 patients underwent ERCP. Therefore, the prevalence of choledochocele was 0.3%. The mean age at the time of diagnosis was 68.5 years (range, 42–86 years). There were seven men and 14 women. As for clinical symptoms, abdominal pain was the most frequent (57%), followed by jaundice (10%). Seven patients (33%) showed no symptoms; ERCP was indicated for the evaluation of other pancreatobiliary changes in six of these patients, and for abnormality in the ampullary region detected at screening esophagogastroduodenoscopy in the other. Laboratory tests demonstrated abnormal GOT/GPT, alkaline phosphatase (ALP)/gamma glutamyl transpeptidase (γ-GTP), and amylase levels in 52%, 48%, and 10% of the patients, respectively. The tumor markers carcinoembryonic antigen (CEA) and carbohydrate antigen (CA)19-9 showed elevation in 10% of patients tested (1/10) and 27% of patients tested (3/11), respectively. The size of the choledochocele ranged from 6 mm to 23 mm, with an average of 14.0 ± 5.6 mm. The diameter of the bile duct ranged from 7 mm to 25 mm, with an average of 13.2 ± 4.8 mm. There was no correlation between choledochocele size and bile duct size.

Configuration of the pancreatobiliary ductal system in choledochocele

The configuration of the choledochocele and pancreatobiliary ductal system was classified into two categories (Fig. 1). In type I, the choledochocele and pancreatic duct were visualized independently or simultaneously, while in type II, the pancreatic duct was visualized after filling of the choledochocele, suggesting the choledochocele itself to be a common channel. The number of patients with each type was 19 (90.5%) and 2 (9.5%), respectively.

Comorbid pancreatobiliary diseases in patients with choledochocele (Tables 1 and 2)

Comorbid pancreatobiliary diseases in patients with choledochocele in this study are shown in Table 1. The benign comorbid diseases included choledocholithiasis ($n = 7$ patients, 4 of whom also had cholecystolithiasis), cholecystolithiasis ($n = 4$), acute pancreatitis ($n = 2$, 1 of whom had choledocholithiasis as well), chronic pancreatitis ($n = 2$), and acalculous cholecystitis ($n = 1$). Biliary malignancy was seen synchronously in three patients (14.3%); two had gallbladder carcinoma and one had bile duct cancer. Two patients had no

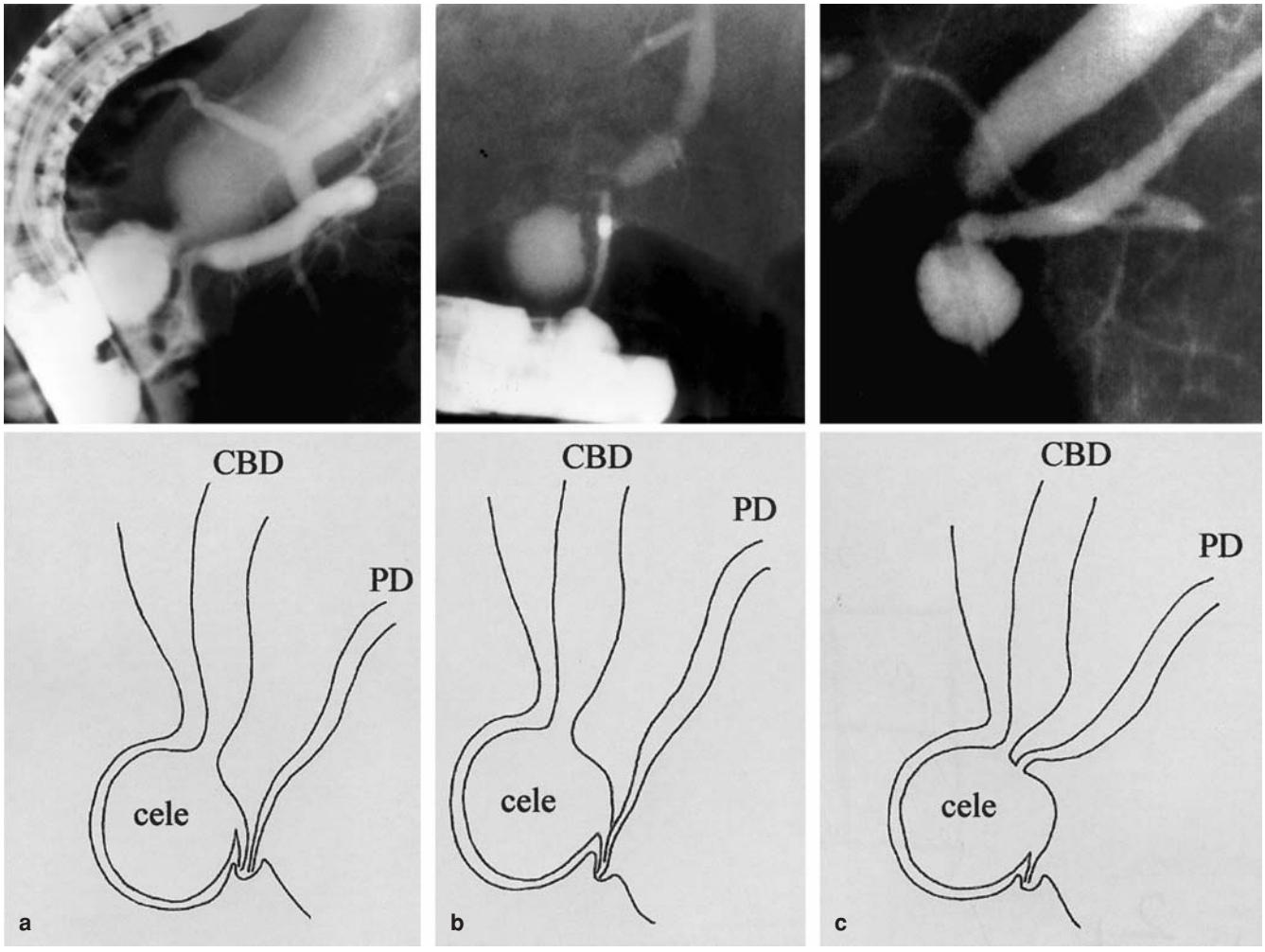

Fig. 1a–c. Classification of configuration of choledochocele (photographs and schemata). In type I (**a, b**), the bile duct terminal forms a choledochocele and opens to the duodenum independently from the pancreatic duct or forms a very short common channel with the duct. In type II (**c**), both the bile duct and the pancreatic duct open into a choledochocele, forming a common channel, and the choledochocele opens into the duodenum. Nineteen of 21 patients (90.5%) showed type I, and 2 patients (9.5%) showed type II. *Cele*, choledochocele; *CBD*, common bile duct; *PD*, pancreatic duct

Table 1. Comorbid pancreatobiliary diseases in patients with choledochocele ($n = 21$)

Malignant	3 (14.3)
Carcinoma of the gallbladder (with cholecystolithiasis, 1)	2 (9.5)
Carcinoma of the bile duct	1 (4.8)
Benign	16 (76.2)
Choledocholithiasis (with cholecystolithiasis, 4)	7 (33.3)
Cholecystolithiasis	4 (19.1)
Acute pancreatitis (with choledocholithiasis, 1)	2 (9.5)
Chronic pancreatitis	2 (9.5)
Acalculous cholecystitis	1 (4.8)
None	2 (9.5)

Numbers in parentheses are percentages

Table 2. Correlation between configurational type of choledochocele and comorbid pancreatobiliary diseases in patients with choledochocele ($n = 21$)

Configurational type	Comorbid diseases (no. of patients)
I	Choledocholithiasis, $n = 7$; cholecystolithiasis, $n = 3$; pancreatitis, $n = 4$; gallbladder cancer, $n = 2$; bile duct cancer, $n = 1$; cholecystitis, $n = 1$; none, $n = 1$
II	Cholecystolithiasis, $n = 1$; none, $n = 1$

Table 3. Amylase levels in the bile of patients with choledochocele

Patient no.	Configurational type	Size of bile duct (mm)	Size of cyst (mm)	Amylase level in bile (IU/l)	Comorbid disease
1.	I	12	8	≦10	Acute pancreatitis
2.	I	7	8	≦10	Chronic pancreatitis
3.	I	20	17	≦10	Choledocholithiasis
4.	I	10	16	24	Gallbladder cancer
5.	I	15	20	825	Gallbladder cancer
6.	I	15	18	1130	Choledocholithiasis
7.	II	7	8	16690	Cholecystolithiasis
8.	I	7	10	66580	Cholecystolithiasis

concomitant diseases. Table 2 indicates the correlation of the type of the configuration of the choledochocele and the bile duct, and comorbid pancreatobiliary diseases. An association with biliary malignancy was seen in the type-I group.

Amylase level in bile in patients with choledochocele

The level of amylase in the bile was measured in eight patients (type I, $n = 7$; type II, $n = 1$), four of whom (50%) showed elevation of the level. One patient had gallbladder cancer, and the amylase level was 825 IU/l, one patient had choledocholithiasis and the amylase level was 1130 IU/l and the other two patients had cholecystolithiasis, with amylase levels in the bile of 16690 IU/l and 66580 IU/l (Table 3). In relation to the type of configuration of the ductal system, elevation of the amylase level in the bile was seen in the one patient with type II, and in three of the seven type-I patients. No correlation was apparent between choledochocele size, bile duct size, and level of amylase in the bile.

Discussion

The definition of choledochocele is not well established, although there have been several proposals.[8,9] In general, enlargement of the oral protrusion of the papilla of Vater and cystic dilatation of the bile duct terminal are considered to be mandatory. However, there are some conditions mimicking choledochocele, such patients with impacted gallstones at the papilla of Vater, the development of cystic change at the bile duct terminal in patients who have undergone endoscopic sphincterotomy for bile duct stones,[8] and some patients with abnormal arrangement of the pancreatobiliary ductal system, which necessitates great care in making the diagnosis.[10] In the present study, we defined the diagnostic criteria of choledochocele as: (1) obvious cystic bulging of the oral protrusion of the papilla of Vater on endoscopy, and (2) cystic dilatation of the common channel or of the bile duct terminal after penetration of the muscularis propria of the duodenum on X-ray.

In the present study, female predominance was observed. However, most reports describe no difference in prevalence by sex.[11,12] Clinical symptoms and laboratory data were not specific for choledochocele, as most patients had comorbid pancreatobiliary diseases. One of our two patients without coexistent disorders in the pancreatobiliary system showed abdominal pain, with liver dysfunction. This may have been due to compression of the bile duct terminal by a choledochocele as pointed out by Cohen and Bernstein.[13]

Although Sholz et al.'s[14] classification has long been used for the morphological classification of choledochocele, there have been cases that are impossible to so classify. Mori et al.[15] and Kagiyama et al.[16] proposed modified classifications. Kamisawa et al.[17] collected case

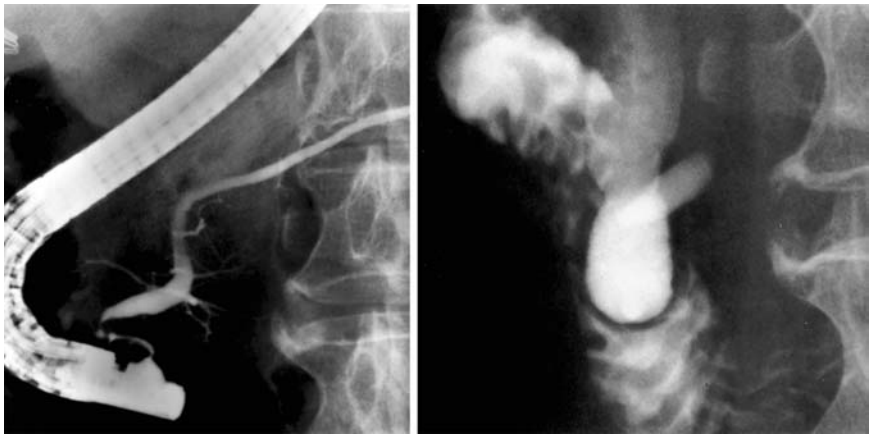

Fig. 2a,b. Endoscopic retrograde pancreatography (ERCP) in a type-I patient. It is obvious from image **a**, taken during cannulation, that the pancreatic duct opens into the duodenum independently from the choledochocele. However, the image in **b**, taken after the filling of both ducts, is similar to an image in a type-II patient

with choledochocele in the literature and proposed a new classification, with three types based on the morphology of the union of the bile and pancreatic ducts: (1) dilation of the common channel, (2) dilation of the bile duct terminal resulting in the formation of a common channel, and (3) dilation of the bile duct terminal without the formation of a common channel. In the in patient group, 33.8% were classified as having a dilated common channel. In contrast, there were only two type-II patients (9.5%) in our study. In our experience, there are quite a few cases in which it is difficult to differentiate type II from type I by interpreting the films taken after the filling of the entire pancreatobiliary ductal system. Figure 2 illustrates this difficulty. If the configuration in the patient shown in Fig. 2 were to have been judged by the findings of a single film, this patient would have been classified as type II, in spite of visualization of the pancreatic duct alone at the first cannulation. Therefore, correct classification based on the interpretation of an image after the filling of the entire pancreatobiliary ductal system is not possible, and judgment of the configuration of the pancreatobiliary ductal system based on the pictures in the literature is inadequate. In the present study, we classified choledochocele into two types based on the serial images obtained at the injection of contrast medium. Type I is considered not to have a common channel or to have a very short common channel. In type II, the pancreatic duct is visualized following filling of the choledochocele that functions as a long, wide common channel. It is conspicuous that there is stasis of pancreatic juice in the choledochocele in type II, and this is a type of abnormal arrangement of the pancreatobiliary ductal system itself.

As for comorbid pancreatobiliary disorders, diseases involving biliary stones constituted the majority of benign diseases.[11,12] There was a case which presented with acalculous cholecystitis. It is speculated that choledochocele alone can cause cholecystitis or cholangitis.[18] Therefore, a therapeutic approach to the choledochocele should be considered in patients showing recurrent biliary infection. We had two patients showing acute pancreatitis (excluding biliary pancreatitis). In the literature, a correlation between choledochoceles and pancreatic comorbidity has been pointed out,[19,20] although the mechanism has not been clarified well. In terms of comorbid biliary malignancies, their prevalence is reportedly 6% to 8%.[3,8] In the present study, 14.3% of the patients had biliary malignancies (two with gallbladder cancer and one with bile duct cancer). The association with biliary malignancy may be more frequent than previously thought. As mentioned above, the type II choledochocele is a form of abnormal arrangement of the pancreatobiliary ductal system. What is interesting is that there were patients who developed biliary malignancy in the type-I group. Elevation of the level of amylase in the bile was observed in 50% of the eight patients in whom measurement was performed, including one patient with biliary malignancy. In a type-II patient, easy reflux of pancreatic juice into the bile duct was confirmed by the elevated amylase level of 16690 IU/l. Additionally, three of the seven type-I patients showed elevation of the level of amylase in the bile, suggesting the presence of a functional short common channel in some type-I patients. In type I of our classification, reflux of pancreatic juice into the bile duct would rarely occur, due to the presence of the sphincter of Oddi. However, Ohtsuka et al.[21] have also reported patients showing elevated levels of amylase in the bile in patients with type I of our criteria, and they have hypothesized the possibility of reflux of pancreatic juice into the choledochocele and bile duct when the pressure in the choledochocele is low. There is another possibility; namely, dysfunction of the sphincter of Oddi, caused by a unique configuration of the pancreatobiliary ductal system, may result in the reflux of pancreatic juice. We had three patients with biliary malignancy

who showed type I. This may also support the possibility of a functionally abnormal arrangement of the pancreatobiliary ductal system in such patients. The higher age of patients with choledochocele and biliary malignancy than that of patients with abnormal arrangement of the pancreatobiliary ductal system[16] and malignancy may reflect a lower degree of reflux of pancreatic juice in the former than in the latter. It is as yet unknown whether choledochocele is congenital or acquired,[22] and the possibility of secondary cystic dilatation derived from insufficiency of the sphincter of Oddi remains.

In conclusion, choledochocele should perhaps be regarded as a functional abnormality of the union of the biliopancreatic ductal system, even though a morphological abnormality causing regurgitation of pancreatic juice into the bile duct is not proven. Fenestration of a choledochocele by endoscopic sphincterotomy (EST) in type-II patients is possibly warranted to prevent the stasis of pancreatic juice in the choledochocele and bile duct. In type-I patients, EST and close follow up may be justified when the level of amylase in the bile is high. Further research should be carried out on the morphology and physiology of choledochocele and its possible association with carcinogenesis.

References

1. Aionso-Lej, Rever WB Jr, Pessagno DJ. Congenital choledochal cyst, with a report of 2 and analysis of 94 cases. Int Abstr Surg 1959;108:1–30.
2. Sasaki M. Choledochal cyst and choledochocele (in Japanese). Clin Gastroenterol 1998;13:1579–83.
3. Shiomi S, Kobayashi S, Nakagawa H, Hayashida Y, Maekawa T, Sakakibara N, et al. A case of choledochocele with carcinoma of the gallader (in Japanese). Jpn J Gastroenterol Surg 1989;22:957–60.
4. Ozawa K, Yamada T, Matumoto Y, Tobe R. Carcinima arising in a choledochocele. Cancer 1980;45:195–7.
5. Ohishi S, Nara K, Satou S, Asano S, Murakami H, Ishigaki H, et al. A case of choledochocele (in Japanese). J Biliary Tract Pancreas 1991;12:515–9.
6. Deguchi H. A case of choledochocele (in Japanese). Gastroenterol Surg 1998;21:247–50.
7. Chatila R, Andersen DK, Topazian M. Endoscopic resection of a choledochocele. Gastrointest Endosc 1999;50:578–80.
8. Kamisawa T, Amemiya K, Tu Y, Egawa N, Okamoto A, Maekawa M. Proposal of diagnostic criteria of choledochocele (in Japanese). J Jpn Biliary Assoc 2001;16:26–32.
9. Park KB, Auh YH, Kim JH, Lee MG, Ha HK, Kim PN, et al. Diagnostic pitfalls in the cholangiograpic diagnosis of choledochocele: cholangiographic quality and its effect on visualization. Abdom Imaging 2001;26:48–54.
10. Inoue S, Matumoto S, Kobayashi T, Ueda J, Ishimitu H, Ongi T, et al. A case of pancreaticobiliary maljunction mimicking choledochocele (in Japanese). J Biliary Tract Pancreas 1998;19:861–4.
11. Munakata M, Murata Y, Murakami H, Ishigaki H, Nakamichi S, Baba T, et al. A case of choledochocele and review of 35 cases from the literatures in Japan (in Japanese). Kan Tan Sui 1991; 23:1053–9.
12. Tajiri H. Choledochocele-containing stones. Am J Gastroenterol 1996;91:1046–8.
13. Cohen F, Bernstein JR. Choledochocele presenting with jaunidice. Dig Dis Sci 1981;26:667–70.
14. Scholz FJ, Carrera GF, Larsen CR. The choledochocele: correlation of radiological, clinical and pathological findings. Radiology 1976;118:25–8.
15. Mori T, Iriyama K, Takenaka T, Teranishi T, Yoshino J. Choledochocele; report of a case and review of the literature (in Japanese). Gastroenterol Surg 1981;4:1851–5.
16. Kagiyama S, Okazaki K, Yamamoto Y, Morita M, Sakamoto Y, Tamura S, et al. Four cases of choledochocele and review of the literature in Japan (in Japanese with English abstract). Gastroenterol Endosc 1986;28:1895–901.
17. Kamisawa T, Tu Y, Egawa N, Ishiwatari J, Okamoto A, Matukawa M. Study of cases with choledochocele, with special emphasis of classification and associated diseases (in Japanese). J Jpn Biliary Assoc 2001;15:104–10.
18. Endo M, Sajima K, Hanawa S, Ito S, Aoki T, Koyanagi Y. A case of choledochocele (in Japanese with English abstract). J Jpn Surg Assoc 2000;61:165–8.
19. Greene FL, Brown JJ, Rubinstein P, Anderson MC. Choledochocele and recurrent pancreatitis. Am J Surg 1985;149:306–9.
20. Imaeda K, Katagiri K, Miyamoto T, Andou T, Tokunaga H, Ide M. A case of choledochocele associated with carcinoma of the pancreas. Dig Endosc 1995;7:71–6.
21. Ohtsuka T, Inoue K, Ohuchida J, Nabae T, Takahata S, Niiyama H, et al. Carcinoma arising in choledochocele. Endoscopy 2001; 33:614–9.
22. Ladas SD, Katsogridakis I, Tassions P, Tastemiroglou T, Vrachliotis T, Raptis SA. Choledochocele, an overlooked diagnosis: report of 15 cases and review of 56 published reports from 1984 to 1992. Endoscopy 1995;27:233–9.