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Differences between residual and primary choledocholithiasis in cholecystectomy patients

José Ruiz Pardo, Andrés García Marín, Francisco Javier Ruescas García, Miguel Jurado Román, Marcelo Scortechini, María Pilar Sagredo Rupérez and Juan Valiente Carrillo

General Surgery and Digestive Diseases Service. Hospital de Hellín. Hellín, Albacete. Spain

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Correspondence: José Ruiz Pardo. General Surgery and Digestive Diseases Service. Hospital de Hellín. C/ Juan Ramón Jiménez, 40. 02400 Hellín, Albacete

e-mail: josrp@hotmail.es

ABSTRACT

Introduction: choledocholithiasis can be primary from stones originally formed in the choledocho or secondary from stones that have migrated from the gallbladder to the choledocho. The objective of this study was to determine the clinical differences between both types of choledocholithiasis in cholecystectomy patients.

Material and methods: a comparative and retrospective study was performed of cholecystectomy patients who presented choledocholithiasis. Residual or secondary choledocholithiasis (group 1) was defined as those which appear in the first two years after cholecystectomy and primary choledocholithiasis (group 2) was defined as those which appear two years after cholecystectomy. Choledocholithiasis was confirmed by endoscopic retrograde cholangiopancreatography (ERCP) or surgery.

Results: patients with primary choledocholithiasis (n = 14) were older (61.5 ± 20.3 *vs* 74.4 ± 10.5 years; p = 0.049) and had a greater body mass index (BMI) (27.7 ± 4.3 *vs* 31.6 ± 4.6 kg/m^2; p = 0.043) and a larger extrahepatic bile duct diameter (10.7 ± 2.7 *vs* 14.7 ± 3.5 mm; p = 0.004) compared to patients with residual or secondary

choledocholithiasis (n = 11). All patients were treated by ERCP. There were no differences between groups 1 and 2 regarding recurrences (36.2 % *vs* 14.3 %; p = 0.350), disease-free survival (64.6 ± 30.9 *vs* 52.2 ± 37.7 months; p = 0.386) and overall survival (73.6 ± 32.4 *vs* 54 ± 41.9 months; p = 0.084).

Conclusions: patients with primary choledocholithiasis were older and had a greater BMI and a larger diameter of the bile duct compared to patients with residual or secondary choledocholithiasis. ERCP is a good therapeutic option for the resolution of both types of choledocholithiasis.

Keywords: Choledocholithiasis. Residual choledocholithiasis. Primary choledocholithiasis. Diagnosis. Treatment.

INTRODUCTION

Choledocholithiasis is classified as primary or secondary (1). Primary choledocholithiasis represents 4-14 % of cases (2,3). In these cases, choledocholithiasis is formed in the bile duct (1,4), occurs several years after cholecystectomy and bile duct stones are brown-pigmented (calcium bilirubin stones) (4). Conversely, secondary choledocholithiasis has migrated from the gallbladder (1,4) and represents 86 % to 96 % of cases (2,3). Bile duct stones are usually cholesterol stones (4). The frequency of choledocholithiasis after cholecystectomy ranges from 1.2 to 14 %, although only 0.3 % of patients will have symptoms (5).

Residual choledocholithiasis is a type of secondary choledocholithiasis that occurs in 2 % of cholecystectomies (6). This manifests after surgery, having previously gone unnoticed or due to surgical manipulation during cholecystectomy (5). Primary choledocholithiasis was defined in 1977 by Saharia et al. as that which occurs two years after cholecystectomy (with or without bile duct exploration) in patients without an elongated cystic stump or biliary stenosis. The stones should be soft, easily crushable, brown or sludge (3). This has even been described 33 years after cholecystectomy (7) and in patients with gallbladder agenesis (8,9).

Choledocholithiasis in cholecystectomy patients is infrequent and there are few references in the scientific literature. Therefore, the aim of this study was to analyze

and compare the characteristics of patients with residual and primary choledocholithiasis, as well as their therapeutic management.

MATERIAL AND METHODS

This was an observational, comparative and retrospective study. The study cohort consisted of cholecystectomy patients who presented choledocholithiasis after cholecystectomy from January 2009 to October 2019. Choledocholithiasis was confirmed by endoscopic retrograde cholangiopancreatography (ERCP) or surgery. The exclusion criteria were: patients with choledocholithiasis prior to cholecystectomy, ERCP prior to cholecystectomy, manipulation of the bile duct during surgery (transcystic cholangiography and/or choledochotomy), iatrogenic bile duct lesions during cholecystectomy, subtotal cholecystectomy or a long cystic stump, post-surgical/inflammatory/tumor stenosis of the bile duct, primary sclerosing cholangitis, gallbladder cancer, choledochal cysts, cirrhosis or other liver diseases, hepatolithiasis, bile duct drainage abnormalities (periampullary tumors, chronic pancreatitis of the head of the pancreas, etc.) and Lemmel's syndrome (obstructive jaundice due to periampullary duodenal diverticulum in the absence of choledocholithiasis or neoplasm) (10) prior to the onset of choledocholithiasis.

The following groups of patients were analyzed and compared:

– *Group 1 (residual choledocholithiasis).* Defined as choledocholithiasis that occurred during the first two years after cholecystectomy in patients who had not presented choledocholithiasis before surgery.

– *Group 2 (primary choledocholithiasis).* Defined as choledocholithiasis that occurred two years after cholecystectomy in patients who had not presented choledocholithiasis before surgery.

Body mass index (BMI), diabetes mellitus, hypercholesterolemia, hypertriglyceridemia, hemolytic anemia, taking oral contraceptives, hormone replacement therapy, type of cholecystectomy (laparoscopic *vs* open), gallbladder histopathology, gallbladder cholesterolosis, gallbladder adenomyomatosis and cholangitis prior to choledocholithiasis and after cholecystectomy were analyzed.

The following laboratory values were analyzed: total bilirubin (normal: 0,3-1,2 mg/dl), direct bilirubin (normal: 0,03-0,30 mg/dl), aspartate aminotransferase (AST) (normal: 10-34 U/l), alanine aminotransferase (ALT) (normal: 10-49 U/l), gamma-glutamyl transpeptidase (GGT) (normal: 10-38 U/l), alkaline phosphatase (normal: 40-150 U/l), amylase (normal: 30-118 U/l), cholesterol (normal: 130-250 mg/dl), LDL cholesterol (normal: 100-150 mg/dl), HDL cholesterol (normal: 45-85 mg/dl), triglycerides (normal: 40-150 mg/dl) and choledocholithiasis diagnosis.

Type of treatment (ERCP or surgery), presence of periampullary diverticulum, extrahepatic bile duct diameter evaluated by cholangiography, placement of biliary and/or pancreatic prosthesis and complications were also analyzed. During the follow-up, recurrence of choledocholithiasis, disease-free survival (DFS) (months), overall survival (OS) (months) and mortality associated with the disease were studied. DFS was defined as the period from the treatment of choledocholithiasis to recurrence.

The collected data were entered into a database. For categorical variables, the data were expressed as frequencies and percentages and compared using the Pearson's Chi-squared test or Fisher's exact test, as appropriate. For continuous quantitative variables, the data were expressed as mean ± standard deviation. The normal distribution of the variables was checked by the Kolmogorov-Smirnov test. The quantitative variables of the groups were compared using the Student's t test for independent data when they followed a normal distribution. In the event that quantitative variables did not follow a normal distribution, the non-parametric Mann-Whitney U test was used for comparisons. The Kaplan-Meier method was used to analyze OS and DFS and the log-rank test for the comparison between groups. A p-value < 0.05 was considered as statistically significant.

RESULTS

Of the patients who met the selection criteria, 44 % (n = 11) had residual choledocholithiasis and 56 % (n = 14) had primary choledocholithiasis. Patients with primary choledocholithiasis were older (61.5 ± 20.3 *vs* 74.4 ± 10.5 years; p = 0.049) and had a greater BMI (27.7 ± 4.3 *vs* 31.6 ± 4.6 kg/m^2; p = 0.043) (Table 1). No patients had hemolytic anemia nor were treated with oral contraceptives or hormone replacement

therapy. The time from cholecystectomy to the appearance of choledocholithiasis was longer in patients with primary choledocholithiasis (6.3 ± 7.5 *vs* 134.3 ± 90.1 months; p < 0.001) (Table 2).

All patients with choledocholithiasis were treated by ERCP. The diameter of the bile duct measured by ERCP cholangiography was larger in patients with primary choledocholithiasis (10.7 ± 2.7 *vs* 14.7 ± 3.5 mm; p = 0.004) (Table 2). There were no differences between groups 1 and 2 regarding biliary prosthesis placement (9.1 % [n = 1] *vs* 7.1 % [n = 1]; p = 1.000), pancreatic prosthesis placement (0 % *vs* 7.1 % [n = 1]; p = 1.000) and post-ERCP complications (a case of pancreatitis in group 2) (0 % *vs* 7.1 % [n = 1]; p = 1.000).

There were no differences between groups 1 and 2 regarding recurrences (36.2 % [n = 4] *vs* 14.3 % [n = 2]; p = 0.350), DFS (64.6 ± 30.9 *vs* 52.2 ± 37.7 months; p = 0.386) and OS (73.6 ± 32.4 *vs* 54 ± 41.9 months; p = 0.084) during a mean follow-up of 62.6 ± 38.6 months. The treatment of recurrences was performed by ERCP and was satisfactory in all cases. No patient died due to the disease.

DISCUSSION

Strict selection criteria were applied in this study in order to perform an accurate analysis between primary choledocholithiasis and residual choledocholithiasis after cholecystectomy. Patients with a suspicion or presence of choledocholithiasis prior to cholecystectomy and manipulation of the bile duct during cholecystectomy (transcystic cholangiography, choledochotomy, etc.) were excluded. Thus, choledocholithiasis did not occur prior to surgery nor was it triggered by additional manipulation of the bile duct during surgery. Patients with ERCP and sphincterotomy prior to surgery were also excluded, since a better drainage of the bile duct could prevent the development of choledocholithiasis. Likewise, patients with any anomaly that could hinder the biliary drainage into the duodenum, producing biliary stasis and favoring the appearance of choledocholithiasis (periampullary tumors, neoplastic, iatrogenic or inflammatory bile duct lesions, choledochal cysts, etc.) were excluded.

Patients with primary choledocholithiasis were older, which could be explained due to the age cut-off in the definition of both pathologies. The factors associated with the

development of biliary lithiasis described in the scientific literature include: female sex, pregnancy, oral contraceptives, hormone replacement therapy, diabetes mellitus, obesity, hypercholesterolemia, hypertriglyceridemia, a low value of HDL cholesterol, recurrent cholangitis and hemolytic anemia, among others (11,12). In this study, only obesity evaluated by BMI was associated with the development of primary choledocholithiasis. In other studies, the presence of a periampullary diverticulum was a risk factor for the development of primary choledocholithiasis (13). The diameter of the extrahepatic bile duct was larger in patients with primary choledocholithiasis. This could be explained due to the fact that in residual choledocholithiasis, the lithiasis is already formed in the gallbladder and migrates to the bile duct without causing a significant dilation. On the other hand, the formation of primary choledocholithiasis would take much longer until its diagnosis and treatment, producing a progressive dilation of the bile duct.

With regard to treatment, ERCP was performed in all patients. A number of complications were consistent with other published studies, where a complication rate of 5-9.8 % after ERCP is described (14,15). On the other hand, the percentage of recurrences was also similar to that found in other studies. For example, the study of Kim et al. (16) reported 21.3 % of recurrences of primary choledocholithiasis. In addition, the factors described in the scientific literature associated with the recurrence of primary choledocholithiasis include a diameter of the extrahepatic bile duct equal to or greater than 13 mm and the location of the papilla on the inner rim or deep within a diverticulum (16).

This is the first study in the scientific literature in which residual and primary choledocholithiasis are compared. However, there is the limitation of the small sample size, therefore the statistical power is lower. Thus, the results must be interpreted with caution.

In conclusion, patients with primary choledocholithiasis are older, and have a greater BMI and a larger diameter of the extrahepatic bile duct compared to patients with residual choledocholithiasis. Furthermore, ERCP is a good therapeutic option for the resolution of both types of choledocholithiasis.

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Table 1. Sociopersonal and clinical variables of the patients with choledocholithiasis

Variables	*Residual choledocholithiasis* (n = 11)	*Primary choledocholithiasis* (n = 14)	*p*
Age (years)	61.5 ± 20.3	74.4 ± 10.5	*0.049*
Gender:			
Masculine	36.4 % (n = 4)	35.7 % (n = 5)	1.000
Feminine	63.6 % (n = 7)	64.3 % (n = 9)	
Diabetes mellitus:			
No	81.8 % (n = 9)	71.4 % (n = 10)	0.661
Yes	18.2 % (n = 2)	28.6 % (n = 4)	
Hypercholesterolemia:			
No	81.8 % (n = 9)	85.7 % (n = 12)	1.000
Yes	18.2 % (n = 2)	14.3 % (n = 2)	
Hypertriglyceridemia:			
No	72.7 % (n = 8)	64.3 % (n = 9)	1.000
Yes	27.3 % (n = 3)	35.7 % (n = 5)	
BMI (kg/m^2)	27.7 ± 4.3	31.6 ± 4.6	*0.043*
Type of cholecystectomy:			
Laparoscopic	100 % (n = 11)	78.6 % (n = 11)	0.230
Open	0	21.4 % (n = 3)	
Gallbladder histopathology:			
Cholelithiasis without cholecystitis	0	28.6 % (n = 4)	0.105
Lithiasic chronic cholecystitis	100 % (n = 11)	71.4 % (n = 10)	
Gallbladder cholesterolosis:			
No	72.7 % (n = 8)	85.7 % (n = 12)	0.623
Yes	27.3 % (n = 3)	14.3 % (n = 2)	
Gallbladder adenomyomatosis:			
No	100 % (n = 11)	92.9 % (n = 13)	1.000
Yes	0	7.1 % (n = 1)	
Cholangitis prior to the diagnosis of			

choledocholithiasis:			
No	90.9 % (n = 10)	92.9 % (n = 13)	1.000
Yes	9.1 % (n = 1)	7.1 % (n = 1)	

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Table 2. Diagnostic and therapeutic variables of the patients with choledocholithiasis

Variables	*Residual choledocholithiasis* (n = 11)	*Primary choledocholithiasis* (n = 14)	*p*
Time from cholecystectomy to the appearance of choledocholithiasis (months)	6.3 ± 7.5	134.3 ± 90.1	*< 0.001*
Clinical manifestations of choledocholithiasis:			
Abdominal pain	45.4 % (n = 5)	50 % (n = 7)	0.851
Abdominal pain and jaundice	27.3 % (n = 3)	28.6 % (n = 4)	
Painless jaundice	9.1 % (n = 1)	14.3 % (n = 2)	
Acute pancreatitis	18.2 % (n = 2)	7.1 % (n = 1)	
Laboratory values:			
Total bilirubin (mg/dl)	2.6 ± 1.9	3.7 ± 2.3	0.227
Direct bilirubin (mg/dl)	1.8 ± 1.6	2.7 ± 1.8	0.196
AST (U/l)	175.5 ± 116.8	271.4 ± 251.6	0.291
ALT (U/l)	280 ± 282.9	315.9 ± 202.9	0.338
GGT (U/l)	714.6 ± 461.5	1,041.9 ± 914.1	0.547
Alkaline phosphatase (U/l)	293.8 ± 247.2	406.1 ± 394.6	0.171
Amylase (U/l)	630.6 ± 1293	147.4 ± 330.7	0.826
Cholesterol (mg/dl)	183.2 ± 43.1	175.7 ± 56	0.718
LDL cholesterol (mg/dl)	107.6 ± 32.1	104.5 ± 41.8	0.847
HDL cholesterol (mg/dl)	47.4 ± 17.7	46.4 ± 16.3	0.884
Triglycerides (mg/dl)	170.8 ± 73.4	143.6 ± 66.4	0.139
Diagnosis:			
TC	36.4 % (n = 4)	28.6 % (n = 4)	
MR Cholangiography	54.5 % (n = 6)	71.4 % (n = 10)	0.435
Endoscopic ultrasound	9.1 % (n = 1)	0	
Maximum diameter of extrahepatic bile duct (mm)	10.7 ± 2.7	14.7 ± 3.5	*0.004*

Periampullary diverticulum:			
No	72.7 % (n = 8)	57.1 % (n = 8)	0.677
Yes	27.3 % (n = 3)	42.9 % (n = 6)	