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Long-term Biliary Complications after Liver Surgery Leading to Liver Transplantation

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Abstract. Chronic biliary obstruction with repeated bouts of cholangitis adversely affects quality of life and may lead to secondary biliary cirrhosis with liver failure. We reviewed our experience with chronic biliary complications after surgical treatment of various diseases that at the end needed a liver transplantation. Twelve patients with previous biliary surgery developed secondary biliary cholangitis, secondary biliary cirrhosis, or both. Seven had surgery for liver hydatid disease by *Echinococcus granulosus*, another four had complicated biliary surgery unrelated to hydatid disease, and one had a history of a traffic accident with liver trauma and hepatectomy with chronic biliary fistula. The repeated cholangitis attacks and in two cases of hydatid disease the development of biliary-bronchial fistulas made these patients' lives miserable. All had had previous surgical procedures that made the transplantation procedure more difficult. Nevertheless, patient survival and graft actuarial survival after liver replacement were 75.0% and 69.2%, respectively, at 5 years.

Persistent biliary obstruction as a consequence of various pathologies or surgical treatment of them may produce secondary biliary cirrhosis (SBC) and sclerosing cholangitis (SSC). SCC means slow but progressive destruction of the intra and extrahepatic biliary tree, with inflammatory thickening and irregular stenosis. The etiology of SSC is varied: surgery; infectious disorders such as acquired immunodeficiency syndrome (AIDS) [1] or ascending cholangitis after biliary surgery; ischemia, as with chemotherapy [2, 3], arterial embolization [4], or liver transplantation [5]; and chemicaltoxicity. A case of sclerosing cholangitis after surgical treatment of an *Echinococcus* cyst was reported for the first time by Warren et al. in 1966 [6]. Subsequently, the relation between liver surgery for *E. granulosus* or the use of formaldehyde or other parasiticides to treat the cyst and the onset of SSC was described by others [7–12]. Intraoperative treatment with parasiticides or the irritating effect of the cyst fluid on the bile duct can produce inflammation and then scars.

Sclerosing cholangitis leads to SBC, with progression to liver failure and portal hypertension [13–16]. The fibrosis draws small lobules, similar in appearance to the pig liver. Bile ducts appear obstructed and fibrotic, and there is bile ductule proliferation with expansion of the portal tracts. Proper cirrhosis is a later stage of chronic biliary obstruction [17]. The usual pattern of extrahepatic obstruction is micronodular because the changes are distributed evenly throughout the liver [18].

Selerosing cholangitis and SBC are unusual indications of liver transplantation (LT). SBC has been the reason for LT in 31 patients in Spain since 1984 up to the end of 1998 (0.7% of 4546 registered patients) [19]. According to the European Liver Transplant Registry (ELTR), 32 patients underwent LT for SBC as the primary disease and 2 more with SBC as the secondary disease before 1988. Since 1988 another 246 recipients have been registered with SBC as the primary disease and other 22 with SBC as the secondary indication [20] among 30,859 patients. Among 16,675 cases of cirrhosis, 6580 were virus-related (40%), 4918 were alcohol-related (30%), 2395 patients had primary biliary cirrhosis (15%), and only 1% had SBC.

Twelve patients with long-term biliary complications after biliary surgery have been treated with LT in our department, which means 1.9% of 627 patients who had 714 transplants in our center from April 1984 to March 2000. Seven of them had liver surgery for hydatid disease caused by *E. granulosus* 2 to 29 years before the procedure, most of them several times (from 1 to 11). Five more patients underwent LT for chronic biliary disease unrelated to hydatid disease: one after liver trauma and the other four after cholecystectomy. The time elapsed between the first operation and LT and other variables such as gender, indication and type of first surgery, presence of hydatid disease, and number of operations before LT are shown in Table 1.

The clinical features of the patients were those of chronic cholestasis with progressive liver failure, intermittent bouts of cholangitis with severe deterioration of the quality of life, or both. Two women with hydatid disease (patients 5 and 12) developed a biliary-bronchial fistula, with irritative cough and bile expulsion by mouth. This lasted for 18 years in the last case until she underwent transplantation. Patient 1 had a traffic accident with numerous

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Table 1. Age, gender, and previous surgery.

Patient no.	Age at first operation	Age at LT (years)	Gender	First surgery (indication)	Hydatid disease	First surgery (procedure)	Operations before LT
1	42	43	M	Liver trauma	No	Hepatectomy	1
2	41	47	F	Cholelithiasis	No	Cholecystectomy	6
3	60	62	M	Cholelithiasis	No	Cholecystectomy	2
4	37	43	F	Cholelithiasis	No	Cholecystectomy	1
5	11	37	F	LHD	Yes	Unknown	4
6	57	63	M	LHD	Yes	CPC, cholecystectomy	3
7	22	24	F	LHD	Yes	CE, atypical hepatectomy	4
8	8	37	M	LHD	Yes	CPC	11
9	39	47	M	LHD	Yes	CPC	3
10	59	62	M	Cholelithiasis	No	Cholecystectomy	2
11	21	26	F	LHD	Yes	CPC	2
12	44	62	F	LHD	Yes	CPC, cholecystectomy, sphincteroplasty	1

LHD: liver hydatid disease; CPC: cyst-pericystectomy; CE: cyst emptying plus parasiticide; LT: liver transplantation.

Table 2. Preoperative laboratory data.

Measurement	Value
Alkaline phosphatase	817.7 ± 317.2 IU/L
GGT	296.9 ± 222.9 IU/L
Bilirubin	10.2 ± 8.7 mg/dl
AST	140.5 ± 64.3 IU/L
ALT	110.0 ± 46.1 IU/L
Prothrombin activity	76.4 ± 18.7%
Albumin	3.6 ± 0.4 g/L

GGT: γ-glutamyltransferase; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

Table 3. Transplantation data.

Parameter	Value
Transfusion (units)	
RBCs	22.7 ± 12.5
FFP	27.1 ± 13.0
Platelets	8.0 ± 6.6
Ischemia time (seconds)	
Cold ischemia time	318.6 ± 77.6
Warm ischemia time	63.6 ± 12.5
Technique	
Venovenous bypass	7/12 (58.3%)
IVC clamping without bypass	2/12 (16.6%)
"Piggy-back"	3/12 (25.0%)
Biliary reconstruction	
Hepaticojejunostomy	11/12 (91.6%)
Choledochocholedocostomy	1/12 (8.4%)
Resected liver weight (g)	1508.9 ± 288.0
PNF	1/12 (8.3%)

RBG: red blood cells; FFP: fresh frozen plasma; IVC: inferior vena cava; PNF: primary nonfunction.

fractures and abdominal trauma. A right hepatectomy was performed, but he developed a chronic biliary fistula, with cholangitis and biliary obstruction. The results of the liver function and coagulation tests prior to LT are summarized in Table 2. It can be seen that basically the most affected parameters are those of cholestasis; liver synthetic function was not as severely affected.

Previous surgery adversely affects the LT procedure, making it technically more demanding and prone to complications. Transfusion requirements may be substantial, as can be observed in Table 3, where other characteristics of LT are also shown. In only one of the patients was biliary reconstruction by choledochocholedochostomy possible. This patient had a permeable common hepatic duct, and intense visceral adhesions preventing the use of jejunum for a Roux-en-Y reconstruction. An average of 1.5 kg per liver specimen reflects cholestatic, nonatrophied organs, in general.

Table 4 depicts the histopathologic data found in the recipients' hepatectomy specimens. Eight patients had features of SSC with ($n = 4$) or without ($n = 4$) SBC, and four more patients had SBC. Other pathologic findings less frequently encountered were intrahepatic abscesses and intrahepatic lithiasis. Patient 4 had findings of congenital liver fibrosis, pathology that has been related to SBC [21]. Four patients had hydatid cysts in the resected liver.

Table 5 shows data related to the postoperative stay and laboratory data. The duration of stay is a reflection of the complicated evolution of some of the patients, related mostly to the difficult procedure in recipients who underwent repeated operations. All the patients received cyclosporine-based immunosuppressive therapy; 9 of 12 (75%) had an acute cellular rejection some time in their evolution. There were two retransplantations: one immediately (5 days) for primary nonfunction (patient 9) and the other 7 years afterward due to chronic rejection (patient 8).

Patient actuarial survival after LT at 1, 3, and 5 years has been 75%; and it is 62.5% at 10 years (Fig. 1). For liver grafts the figures are 69.2%, 69.2%, 69.2%, and 46.1%, at 1, 3, 5, and 10 years, respectively. There was one perioperative death (brain hemorrhage after re-LT in patient 9) in the group with hydatid disease, and none in the other group. There were three other deaths, at 6 months (patient 5), 8 months (patient 4), and 6 years (patient 6). Casualties were due to (1) pulmonary embolism; (2) portal rethrombosis with encephalopathy, ascites, and hepatorenal syndrome; and (3) sepsis. There were no deaths after 1991.

The survivals obtained have been similar to those registered at the ELTR and the Registro Espanõ1 de Transplante Hepatico(RETH). Thus, actuarial survivals of patients with LT for SCB at the ELTR at 1, 3, 5, and 10 years were, respectively, 75%, 71%, 69%, and 61%. At the RETH, for 29 patients with follow-up, the respective figures were 77%, 72%, 72%, and 58%.

These survival results are comparable to those obtained for LT due to other etiologies of cirrhosis. With SSC and SBC as secondary conditions, one important advantage is the impossibility of recurrence of the original disease in the graft. The organic consequences of iatrogenic damage to the biliary tree are removed

Table 4. Resected specimen histology.

Patient	Histopathologic description			Hydatid cyst present
	SBC	SSC	Other	
1	+	−	Acute and chronic cholangitis, biliary fistula	—
2	+	−	Acute and chronic cholangitis	—
3	−	+	Acute cholangitis, intrahepatic lithiasis, intrahepatic abscesses, cholangiectasias, portal fibrosis	—
4	−	+	Congenital liver fibrosis, acute cholangitis, biliary fibrosis, hepatocellular adenoma (4), portal thrombosis	—
5	−	+	Lithiasis, multiple liver abscesses	No
6	+	+		Yes
7	+	+	Nodular deformity	Yes
8	+	−	HCV cirrhosis, hepatocellular carcinoma	Yes
9	+	+	Partial nodular transformation, diffuse regenerative nodular hyperplasia	Yes
10	+	−	Ductopenia	—
11	−	+	Hepatolithiasis, bridging fibrosis	No
12	+	+		No

SBC: secondary biliary cirrhosis; SSC: secondary sclerosing cholangitis; +: present; −: absent.

Table 5. Postoperative stay and laboratory data.

Parameter	Value
ICU stay	6.2 ± 6.3 days
Ward stay	31.3 ± 18.1 days
Maximum AST	807.7 ± 592.1 IU/L
Maximum ALT	507.9 ± 413.6 IU/L
Maximum bilirubin	7.8 ± 3.9 mg/dl
Third day AST	78.0 ± 44.0 IU/L
Third day ALT	218.0 ± 92.8 IU/L
Third day prothrombin time	72.5 ± 18.0 IU/L

ICU: intensive care unit.

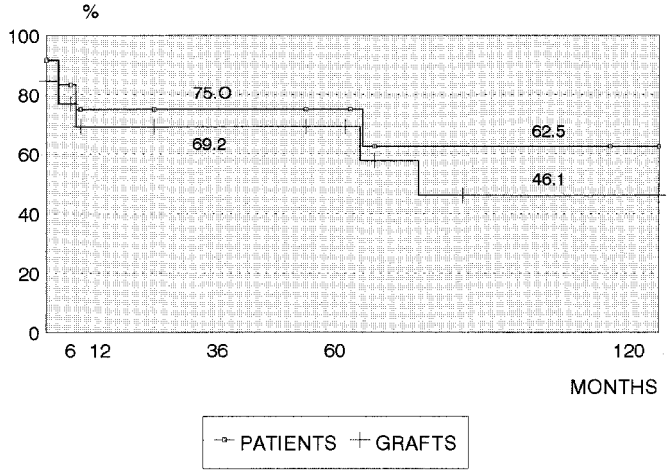

Fig. 1. Actuarial survival after liver transplantation.

with the specimen during LT. In the same way, the results after LT in patients with complications due to *E. granulosus* are satisfactory [22, 23], and there have been no reports of graft infestation. This allows us to use liver grafts after resecting calcified hydatid cysts from the specimen [24]. In contrast, *E. multilocularis* disease recurrence is not rare after LT, darkening the prognosis [25].

In general, patients with SSC and SBC are difficult candidates from the point of view of surgical technique. Once they pass the postoperative period, however, their prognosis is good, as they are not exposed to disease recurrence.

Résumé

L'obstruction biliaire chronique, accompagnée de crises répétées de cholangite,retentit sévèrement sur la qualité de vie du patient et peut se solder par une cirrhose biliaire secondaire avec insuffisance hépatique. Nous avons revu notre expérience avec des complications biliaires chroniques postchirurgicales, de diverses étiologies, qui ont fini par nécessiter une transplantation hépatique. Douze patients ayant des antécédents de chirurgie biliaire ont développé une cholangite sclérosante et/ou une cirrhose biliaire secondaire. Sept avaient eu une chirurgie pour kyste hydatique (Echinococcus granulosus), quatre autres, une complication en rapport avec la maladie kystique du foie et un, un traumatisme du foie par accident de la voie publique, traité par hépatectomie et suivi de fistule biliaire chronique. La répétition des crises de cholangite et dans deux cas, de fistule biliobronchiale à l'occasion du kyste hydatique, a sérieusement atteint la qualité de vie de ces patients. Tous avaient eu des antécédents chirurgicaux, ce qui a compliqué la transplantation. Néanmoins, la survie actuarielle des patients et des greffons après transplantation hépatique est de 75% et de 69.2% à 5 ans.

Resumen

La obstruceión biliar crónica con episodios repetidos de colangitis afecta adversamente la calidad de vida y lleva a la cirrosis biliar con fallo hepático. Hemos revisado nuestra experiencia con las complicaciones biliares crónicas, luego del tratamiento quirúrgico de diferentes enfermedades que finalmente requirieron trasplante del higado. Doce pacientes con cirugia biliar previa desarrollaron colangitis biliar secundaria y/o cirrosis biliar secundaria. Siete tuvieron cirugia por enfermedad hidatidica por Echinococcus granulosus, quatro tuvieron cirugía biliar complicada no relacionada con enfermedad hidatídica y uno tenía historia de un accidente de tráfico con trauma del hígado y hepatectomía con fistula biliar crónica. Los ataques repetidos de colangitis, y en dos casos de enfermedad hidatídica con desarrollo de fistulas bilio-bronquiales, hicieron miserable la vida de los pacientes. Todos habian sido sometidos a procedimientos quirúrgicos previos que dificultaron el trasplante. Sin embargo, las tasas de supervivencia a cinco años del paciente y del trasplante fueron 75% y 69.2%, respectivamente.

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