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Intrahepatic biliary lesions after orthotopic liver transplantation

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Abstract Intrahepatic biliary lesions (IBL) are rare (2–9%) after orthotopic liver transplantation (OLT). The aim was to evaluate the incidence, etiology and outcome. In nine years, a total 532 OLTs were performed in 481 patients. Twenty-four patients developed IBL. Eight were due to HAT, seven to ABOI, three to CDR and six to PI. The time until diagnosis of HAT is longest in patients (14 ± 6) with IBL. ABOI is another cause of IBL. CDR is a rare cause of IBL, however when it takes place, patients must undergo Rtx. Finally, PI is a relevant cause of IBL. In order to suppress the incidence of IBL we should consider 1) the systematic use of Doppler-Ultrasound; 2) emergency reoperation of patients with HAT, 3) avoid ABOI in OLT; 4) Rtx in cases of CDR, and 5) OLT should still be performed as an emergency procedure.

Keywords Liver · Lesions · Biliary

Abbreviations *ABOI* ABO-incompatible blood group donors · *CDR* Chronic ductopenic rejection · *DUS* Duplex ultrasound exploration · *ER* Emergency revascularization · *HAT* Hepatic artery thrombosis · *IBL* Intrahepatic biliary lesions · *OLT* Orthotopic liver transplantation · *PI* Preservation injury · *Rtx* Retransplantation

Introduction

Orthotopic liver transplantation (OLT) is well established as the most effective therapeutic option for patients with acute or chronic end-stage liver disease. Improved patient selection, operative technical advances, and developments in immunosuppression have improved 1-year survival rates after transplantation in at least 80% of the patients at most centers [10]. Despite these good results, biliary complications persist as a significant cause of morbidity and mortality.

Intrahepatic biliary lesions (IBL), which are characterized by non anastomotic biliary strictures and dilatations that involve only the graft, (Fig. 1) [19, 23] were first described in liver transplantations as being associated with ischemia, secondary to hepatic artery thrombosis, (HAT) [16] the incidence ranging from 2–10% of liver recipients [2, 11]. IBL is a relatively late complication, usually diagnosed between 1 and 4 months after OLT.

Recently, other etiologies have been associated with this type of biliary lesions, in which ischemia is one of the major factors. IBL has been related to ABO incompatible blood group donors (ABOI), in which ABH antigen expression in the intrahepatic biliary system of the hepatic allograft may continue and thus may be more susceptible to immunologic injury and subsequent bile duct damage after transplantation across the ABO barrier [17, 22]. Chronic ductopenic rejection (CDR) has also been suspected of being a cause of intrahepatic biliary stricture. CDR causes histological changes of chronic obliterative arteriopathy, and it has been postulated that the resulting bile duct ischemia leads to duct loss and biliary strictures that may be seen on cholangiography [2, 6, 10, 11, 13]. Finally, prolongation of liver allograft ischemia time prior to implantation has been

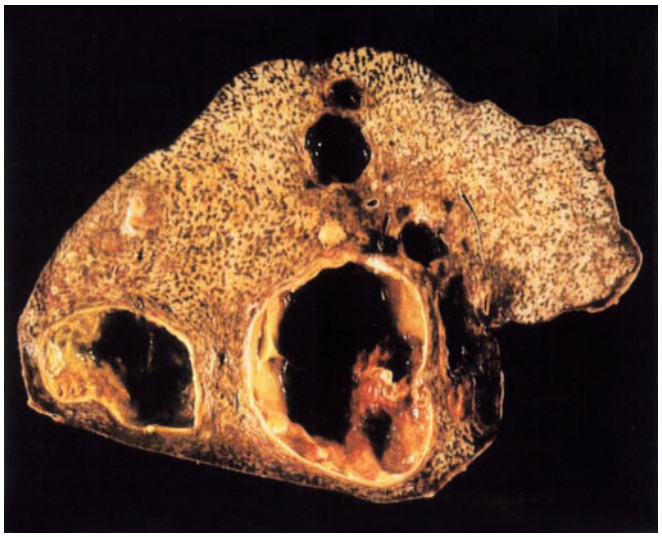

Fig. 1 Dilatation of biliary tract with calcified biliary material occupying the lumen, significant cholestasis in the hepatic parenchyma

shown to be one of the most important risk factors for the occurrence of IBL following transplantation, suggesting that this complication might be due to preservation injury (PI) associated with harvest and implantation [20]. Although the etiology of IBL appears to be clarified, the clinical importance of this complication has not been characterized. The aim of this study was to evaluate the incidence, etiology, diagnosis and management of intrahepatic biliary lesions after liver transplantation.

Patients and methods

From June 1988 to August 1997, 532 liver transplantations were performed in 481 adult recipients at our institution. Eighty-five grafts (14%) did not survive longer than 30 days and were not included in this study.

During this nine year period, 447 recipients were retrospectively analyzed for this study. Twenty-four patients had IBL (4,5%) diagnosed between the first and the sixth month after OLT. Diagnosis of IBL was made with a T-tube cholangiogram in 20 patients (83%) within the first three months, and with endoscopic retrograde cholangiography in 4 patients (17%).

Our group defines IBL as stenotic lesions predominantly localized in hepatic hillium not related to the anastomosis. These lesions may involve the disseminated intrahepatic biliary tract. The cause of the lesions in all patients included in this study is recognized in the literature as being able to produce such lesions.

IBL were due to hepatic artery thrombosis in eight patients, ABO-incompatible (ABOI) liver grafts in seven patients, (4 group 0 patients received group A grafts; 2 group 0 patients received group B grafts; 1 group A patient received a group B graft). Chronic rejection was diagnosed in three patients, all patients developed acute rejection, which was treated with a bolus of corticoids and a corticoid recycling schedule, as established in the treatment protocol for acute rejection [14]. The patients responded badly to treatment, showing a progressive deterioration of their hepatic function. A liver biopsy disclosed in the three patients histological lesions of chronic rejection.

The last group of six patients showed IBL with permeable hepatic artery with no histological signs of rejection. Since no other cause justified the appearance of intrahepatic biliary tract lesions, these patients were included in the group with preservation injury (Fig. 2).

In addition, all patients with HAT (18), ABOI liver transplantation (13), and chronic rejection (13) were included, although they did not develop IBL. Furthermore, in order to compare grafts with preservation injury, a matched control group of 80 patients was selected according to primary liver disease and recipient age. The following potential risk factors were analyzed: in the donors; age, intensive care unit (ICU) stay, ischemia time, and type of pres-

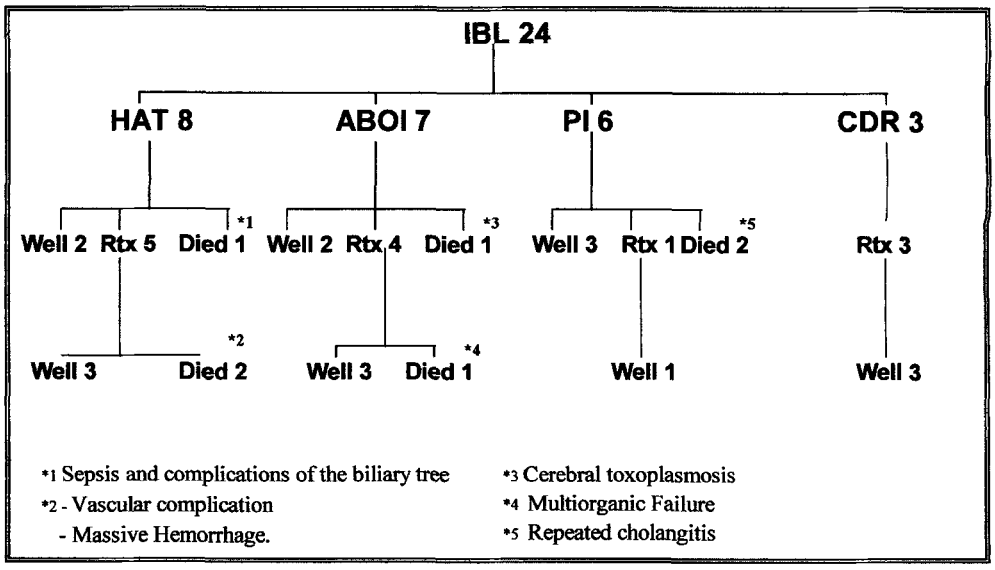

Fig. 2 *IBL* Intrahepatic biliary lesions, *HAT* hepatic artery thrombosis, *CDR* chronic ductopenic rejection, *PI* preservation injury, *Rtx* retransplantation

Table 1 Description of patients included in the study. *RBC* Red blood cells, *PBC* primary biliary cirrhosis

Parameters	IBL ($n = 24$)	No IBL ($n = 124$)	P
DONOR			
Age of donor	39,7 ± 17,8	39,6 ± 18,4	NS
Ischemia time	421 ± 198	368 ± 142	NS
Donor ICU stay	4,2 ± 6,05	2,7 ± 2	0,02
Preservation solution			
Collins	0 (0%)	6 (5%)	NS
Collins + Wisconsin	7 (29%)	18 (18%)	NS
Wisconsin	17 (71%)	100(77%)	NS
RECIPIENT			
Age of Recipient	45 ± 13	44 ± 13	NS
Sex M/F	14/10	82/42	NS
Diagnosis			
HCV Cirrhosis	10	35	NS
HBs Ag Cirrhosis	1	8	NS
Cryptogenic Cirrhosis	0	9	NS
Alcoholic Cirrhosis	5	26	NS
PBC	0	6	NS
Sclerosing Cholangitis	1	4	NS
Acute liver failure	3	30	NS
Retransplantation.	3	6	NS
SURGICAL TECHNIQUE			
RBCs (units)	8,5 ± 10	8,6 ± 10	NS
Platelets (units)	7,3 ± 7,8	6,1 ± 7,6	NS
Piggyback of cave vein	16 (59%)	100 (82%)	NS
Bypass	6 (22%)	13 (10%)	NS
Type of arterial anastomosis			
Hepatic artery to hepatic artery	19(73%)	11 3 (89%)	NS
Hepatic artery to aorta artery.	5 (27%)	11 (11%)	NS
Biliar anastomosis			NS
Hepatic-hepatic	21 (87%)	121 (96%)	NS
Hepatic-jejunostomy	3 (13%)	3 (4%)	NS
Acute rejection	19 (70%)	80 (63%)	NS

ervation solution. In the recipient; age, length of surgery, blood component requirements, incidence of cellular rejection, type of biliary reconstruction, and type of hepatic artery anastomosis. After undergoing transplantation, all the patients were submitted to duplex ultrasound (DUS) exploration within the first 24–48 h. If the arterial flow was not considered adequate, the DUS was repeated after a further 24 h. Moreover, all patients were also submitted to at least two T-tube exploration cholangiographies; one, 10 days before closing the tube, and the other, 3 months before T-tube removal.

Statistical analysis was performed with the Fisher's exact test. Data are expressed as mean ± SE.

Results

Table 1 shows the demographic characteristics of the two groups. Of the 24 patients, 4 died while waiting for retransplantation – 3 due to a cause directly related to IBL, and 1 due to cerebral toxoplasmosis. Thirteen patients (54,2%) underwent retransplantation Rtx) at a mean time of 8,5 months. Three of these died after Rtx, one due to HAT, another due to massive hemorrhage, and the third due to multiple organ failure. Seventeen (70,8%) are alive and well at a mean follow-up age of 46 months, seven with their original IBL (asymptomatic).

Compared with the matching control group (Table 1), these 24 patients showed no differences, regardless if they were donors or recipients, except for the period of donor ICU stay, which was significantly longer in recipients who developed IBL (4,2 ± 6 vs. 2,7 ± 2). Although the total graft ischemia time was longer in patients who developed IBL, the difference was not significant (421 ± 198 vs. 368 ± 142).

Table 2 Hepatic artery thrombosis. *RB* Red blood cells, *HAT* hepatic artery thrombosis, *ICU* intensive care unit, *IBL* ischemic biliary lesions

PARAMETERS	IBL ($n = 8$)	no IBL ($n = 18$)	P
DONOR			NS
Age (years)	43 ± 18	37 ± 20	NS
Ischemia time (min)	438 ± 237	386 ± 123	NS
ICU stay (days)	3,4 ± 3,5	3,6 ± 2,4	NS
RECIPIENT			NS
Age (years)	49 ± 11	45 ± 11	NS
Operative time (min)	378 ± 106	403 ± 117	NS
RBCs (units)	11,3 ± 15,9	15,3 ± 16,3	NS
Platelets (units)	8,2 ± 9	8,3 ± 9,7	NS
Day intervention HAT	14 ± 6	3 ± 2	0,0004

Role of hepatic artery thrombosis in IBL

HAT was documented in 26 of 447 grafts (5,8%). Eighteen were early HAT (within the first 20 days) and eight (22,5%) were late HAT. Patients with early HAT underwent emergency revascularization (ER), in sixteen, (88,8%) the procedure was successful. However, five developed IBL (with the hepatic artery remaining permeable). Furthermore, out of the eight late HAT, which were not treated, three developed IBL. Out of these eight patients with IBL, two remain well and are asymptomatic, one died while waiting for an Rtx, and five underwent transplantation.Two of these patients died in the immediate postoperative period. (Fig. 1). When we compared the group of patients who developed HAT with and without IBL (Table 2), only the time the diagnosis was made significantly differed (14 ± 6 vs. 3 ± 2, $P = 0,0004$).

Table 3 Preservation injury in relation to control match group ($n = 86$). *RBC* Red blood cells, *HAT* hepatic artery thrombosis, *ICU* intensive care unit, *IBL* ischemic biliary lesions

PARAMETERS	IBL ($n = 6$)	Control ($n = 80$)	P
DONOR			
Age (years)	49 ± 19	41 ± 18	NS
Ischemia time (min.)	485 ± 160	367 ± 198	0,05
ICU stay (days)	7,9 ± 11	2,6 ± 2,2	0,0001
RECIPIENT			
Age (years)	53 ± 5	42 ± 10	NS
Operative time (min.)	425 ± 67	397 ± 108	NS
RBCs (units)	7,3 ± 6,5	5,8 ± 4,8	NS
Platelets (units)	3,5 ± 5	4,5 ± 6	NS

Role of the ABO-incompatible livers in IBL

Out of 447 OLTs performed at our institution, twenty patients (4,4%) underwent emergency ABO-incompatible liver transplantation. Seven developed IBL (35%). The time course for the development of progressive biliary strictures and dilatations in these patients has already been widely described in the literature [7, 21]. Of the seven, two are alive and well with asymptomatic IBL. One died while waiting for an Rtx, and four underwent Rtx. Of these four patients, one died due to multiple organ failure (Fig. 1). Five out of seven are alive and well. When we compared ABOI recipients with and without IBL, there was no difference in any of the parameters studied. The incidence of acute rejection episodes, as well as that of corticosteroid resistant rejection episodes, was similar in both groups. Similarly, the type of donor/recipient incompatibility was not related to IBL.

Role of chronic cellular rejection in IBL

Chronic rejection developed in a total of 16 patients (3,5%). Three had ductopenic chronic rejection with IBL. All underwent Rtx and remain well at a mean follow-up age of 41 months. When we studied potential (donor and recipient) factors of IBL, no difference was found between patients who developed IBL and those who did not.

Role of preservation injury in ischemic biliary lesions

In six patients we were not able to find any cause for the development of IBL. We then considered these patients as having a severe preservation injury (PI). Two of them died while waiting for Rtx, one underwent retransplantation, and three are alive and asymptomatic despite the presence of IBL. Four out of six are alive and well after a mean follow-up time of 5 years. When we compared these patients with a matched control group, we found that donor ICU stay (8 ± 11 vs. 3 ± 2) as well as the total ischemia time (485 ± 160 vs. 367 ± 149; $P < 0.05$) were significantly longer in patients who developed IBL. Recipient variables were similar in both groups (Table 3).

Discussion

IBL is a complication that appears early during the immediate postoperative period, although it is diagnosed late in the course of the first three months [20]. The incidence of IBL ranges from 11–19% [6] and is related to a substantial cause of morbidity (50–75%), characterized by the presence of repeated episodes of cholangitis and the necessity for Rtx (35–50%) [20]. A significant rate of mortality (25–40%) and increased cost are also associated with this complication. The overall incidence of IBL in our series was relatively low (24 of 447; 5,4%), however the associated morbidity (66%), Rtx rate (13 of 24; 54%) and mortality (7 of 24; 29%) were similar to those reported in the literature. The etiology is related to HAT, ABO incompatibility, ductopenic chronic rejection, and preservation injury [2, 8, 19, 20]. The role of hepatic artery thrombosis in the development of IBL has already been described [15, 24, 25]. In this study, we confirm the results of Pinna et al., [16] showing the importance of emergency revascularization to avoid a significant percentage of Rtx (9 of 18; 50%) [16]. Furthermore, we demonstrate the value of immediate postoperative ultrasound examination in the early diagnosis of HAT, since a fast diagnosis is of crucial importance for successful and complete revascularization of the graft [9, 12, 16]. Although graft revascularization was successful in 16 of 18 cases, (five finally developed IBL), it is interesting to note that the time until diagnosis was significantly shorter in patients for whom revascularization was not associated with IBL. At our institution, initial immediate postoperative care has included the practice of a Doppler Ultrasound (DUS) within the first 24–48 h, from the very beginning of the study (June 1988). All patients are submitted to DUS postoperatively, and arteriography is performed in difficult cases where the artery cannot be seen. All these procedures are performed despite normal or nearly normal liver function.

The incidence of IBL in liver transplantation across the ABO barrier is very high. This fact has already been pointed out previously in the literature, with values ranging from 20–82%. In a previous study we reported an incidence of IBL of 57% (4 of 9 cases); [7] with the incidence in the present study being 50% (7/14), since 6 out of the 20 ABOI patients died during the first 30 days post-transplant. Therefore, it may be

suggested that with the use of an ABOI liver, 50% of the patients may develop IBL. These results confirm our early experience that emergency incompatible liver grafts are associated with a high morbidity and Rtx rate, and should be avoided whenever possible. The use of artificial devices may play an important role in the future in order to prepare these patients for transplantation or even avoid it [5, 18].

The prevalence of chronic rejection in patients with IBL is not clear. Some authors have observed no association between IBL and chronic rejection [4]. However, others suggest that chronic rejection is associated with chronic obliterative arteriopathy, and it has been postulated that the resulting bile duct ischemia may lead to duct loss and biliary stricture [14]. In our experience, the overall incidence of chronic ductopenic rejection (CDR) is 3,6%, within which the prevalence of IBL rises to 19%. Interestingly, patients with CDR that did not develop IBL and did not undergo Rtx (7 of 13 in our study) died within the following 24 months. We conclude that chronic rejection with or without IBL should be an indication for Rtx, since 7 out of the 9 patients who underwent Rtx are alive and well after a mean follow up of 36 months (one patient died due to multiple organ failure, and the other, due to chronic rejection while awaiting Rtx).

Finally, IBL were reported in six patients without any apparent cause. It is interesting to find that these patients had a significantly longer period of total ischemia, compared with a matching control group of patients. This fact is in accordance with reports in the literature and is considered a major factor in preservation injury [13]. However, it is important to note that at our institution, OLT has always been performed on an emergency basis and within a very short period of time (a means of 8 h). More importantly, since we have not been able to find any other donor factor (except for donor ICU stay), and there is no evidence in the literature of any possibility to identify such "marginal" donors [1, 3], we continue to consider OLT as an emergency procedure, in order to reduce preservation injury to a minimum. In our experience, the role of interventional radiology has been very limited, only 5 patients were submitted to stents procedures. Two of these patients died due to repetitive episodes of cholangitis, a further two underwent retransplantation, and only one is alive and well after stenting of the biliary tree after more than five years. We think that intervention radiology should not be used for this type of patient, since the incidence of cholangitis significally increases [22]. In contrary to experiences by others, we cannot consider it a definitive procedure. The experience of the Mayo Clinic shows that almost 50% of their patients were either re-stented or submitted to retransplantation with a relatively short follow up. However in isolated stenosis of the hilium, the use of expandable metallic stents could represent a therapeutic alternative.

In summary, the incidence of IBL after OLT is relatively low. However, it is associated with very high morbidity and mortality. In order to maintain a low incidence of IBL, we should consider the following: 1. the systematic use of Doppler-Ultrasound immediately after liver transplantation; 2. emergency reoperation of patients in whom HAT is suspected; 3. the avoidance of ABOI liver transplantation; 4. Rtx whenever the diagnosis of chronic rejection is made and, 5. OLT should still be performed on an emergency basis, in order to maintain the total ischemia time to the lowest level possible.

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