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Causes and consequences of ischemic-type biliary lesions after liver transplantation

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Abstract
Biliary complications are a major source of morbidity, graft loss, and even mortality after liver transplantation. The most troublesome are the so-called ischemic-type biliary lesions (ITBL), with an incidence varying between 5% and 15%. ITBL is a radiological diagnosis, characterized by intrahepatic strictures and dilatations on a cholangiogram, in the absence of hepatic artery thrombosis. Several risk factors for ITBL have been identified, strongly suggesting a multifactorial origin. The main categories of risk factors for ITBL include ischemia-related injury; immunologically induced injury; and cytotoxic injury, induced by bile salts. However, in many cases no specific risk factor can be identified. Ischemia-related injury comprises prolonged ischemic times and disturbance in blood flow through the peribiliary vascular plexus. Immunological injury is assumed to be a risk factor based on the relationship of ITBL with ABO incompatibility, polymorphism in genes coding for chemokines, and pre-existing immunologically mediated diseases such as primary sclerosing cholangitis and autoimmune hepatitis. The clinical presentation of patients with ITBL is often not specific; symptoms may include fever, abdominal complaints, and increased cholestasis on liver function tests. Diagnosis is made by imaging studies of the bile ducts. Treatment starts with relieving the symptoms of cholestasis and dilatation by endoscopic retrograde cholangiopancreaticography (ERCP) or percutaneous transhepatic cholangiodrainage (PTCD), followed by stenting if possible. Eventually up to 50% of the patients with ITBL will require a retransplantation or may die. In selected patients, a retransplantation can be avoided or delayed by resection of the extra-hepatic bile ducts and construction of a hepaticojejunostomy. More research on the pathogenesis of ITBL is needed before more specific preventive or therapeutic strategies can be developed.

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Key words Liver transplantation · Ischemic-type biliary lesions · Nonanastomotic strictures · Risk factors

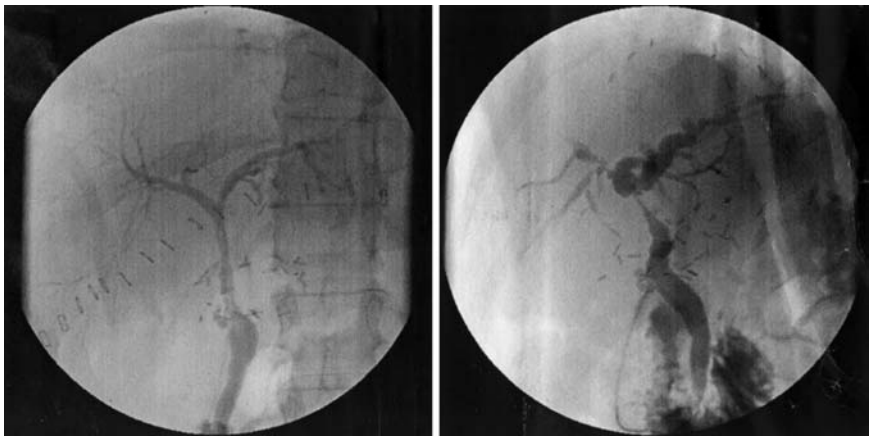
Introduction

Biliary complications have long been recognized as a major cause of morbidity and graft failure in patients after orthotopic liver transplantation (OLT).[1–3] Bile leakage and bile duct strictures are the most common complications. According to their localization, strictures can be classified as anastomotic or nonanastomotic. Nonanastomotic intrahepatic strictures (NAS) are considered to be the most troublesome biliary complication. NAS were first described in OLT associated with hepatic artery thrombosis, where the biliary tree becomes ischemic and eventually necrotic, resulting in a typical cholangiographic picture of biliary strictures, dilatations, and intraductal cast formation.[4] However, these cholangiographic abnormalities of strictures and dilatations can also be seen in patients who do not have hepatic artery thrombosis,[5,6] so the term "ischemic-*type*" biliary lesions (ITBL) emerged (Fig. 1).

The reported incidence of ITBL differs greatly between different series, ranging from 1% to 19%.[7,8] Variations in the definitions of ITBL used in different studies, as well as the reporting of only symptomatic patients, can at least partly explain these differences. In the majority of series, an incidence of 5% to 15% is reported.[9–16]

Etiology and risk factors

The exact pathophysiological mechanism of ITBL is still unknown. However, several risk factors of this often cumbersome complication have been identified, strongly suggesting a multifactorial origin (Table 1). In general, risk factors for ITBL can be divided into three



a **b**

Fig. 1a,b. Cholangiograms 4 months after orthotopic liver transplantation (OLT). **a** Normal; **b** ischemic-type biliary lesions (ITBL)

Table 1. Risk factors for the development of ITBL

Ischemic injury
Warm ischemia in the donor
Prolonged cold ischemia
Reperfusion injury
Warm ischemia during implantation
Disturbed blood flow in the peribiliary plexus
Immunological injury
ABO incompatibility
Pre-existing disease with autoimmune component
Autoimmune hepatitis
Primary sclerosing cholangitis
Cytomegalovirus infection
Chronic rejection
Chemokine polymorphism *CCR5 delta 32*
Bile salt-induced injury
Hydrophilic bile salts are cytoprotective
Hydrophobic bile salts are cytotoxic

ITBL, ischemic-type biliary lesions

different categories: ischemia-related injury to the biliary epithelium; imunologically mediated injury; and cytotoxic injury, induced by bile salts. These categories may point towards different etiological mechanisms of ITBL, as will be described below.

Ischemic injury

The similarities between the radiological abnormalities of ITBL and the bile duct lesions seen in the presence of hepatic artery thrombosis strongly suggest an ischemic factor in the origin of ITBL. The quest for pathogenic mechanisms, therefore, started with factors associated with ischemia.

Cold ischemic and reperfusion injury

Multiple studies have indicated that prolonged cold ischemia time (CIT) predisposes the graft to the development of ITBL.[6,15,17–20] In 1992, Sanchez-Urdazpal et al.[6] reported an incidence of ITBL of 2% in livers with a CIT of less than 11.5 h, rising to 35% in livers with a CIT between 11.5 h and less than 13 h, and even up to 52% in grafts with a CIT of more than 13 h. Nowadays many centers therefore try to keep the CIT below 10 h. However, even with a CIT shorter than 10 h, Guichelaar et al.[17] have shown that the duration of cold storage is still a risk factor for the development of ITBL. The strong positive correlation between CIT and ITBL can be explained by either direct ischemic injury of the biliary epithelium; increased susceptibility of the biliary epithelium to a second factor, such as reoxygenation injury; or secondary ischemia of the biliary epithelium, due to damage to the peribiliary arterial plexus.[6]

The hypothesis that reperfusion injury during OLT contributes to bile duct injury is supported by data provided by the experimental work of Noack et al.[21] Using cell cultures, Noack has shown that biliary epithelial cells are more susceptible to reperfusion/reoxygenation injury than hepatocytes. In an anoxic environment, bile duct epithelial cells and hepatocytes showed equally reduced levels of ATP. However, the rate of cell death after reoxygenation was significantly higher in the bile duct epithelial cells, compared to hepatocytes. Increased production of reactive oxygen species by bile duct epithelial cells, as well as a lower intracellular concentration of glutathione as antioxidant, may explain this difference.[21] Clinical evidence for a contributing role of preservation injury is provided in a clinical study by Li et al.[20] These investigators have shown that the incidence of ITBL is significantly increased in livers with increased preservation injury, as reflected by postoperative peaks in serum aspartate aminotransferase and alanine aminotransferase.[20]

Injury of the peribiliary vascular plexus

Preservation injury results in increased arterial resistance and may cause circulatory disturbances in small capillaries, such as the biliary plexus.[20] Because the blood supply to the biliary tract is solely dependent on

arterial inflow, disturbances in the blood flow through the peribiliary plexus may result in insufficient preservation and subsequent damage of the biliary epithelium.

Several studies have indicated that the viscosity of preservation solutions may play a role in the development of ITBL.[22,23] The highly viscous University of Wisconsin (UW) preservation solution, now routinely used in most centers, might not completely flush out the small donor peribiliary arterial plexus. Microcirculatory disturbances in the peribiliary plexus may lead to obstruction and subsequently result in insufficient bile duct preservation.[23] Strengthening of evidence that insufficient perfusion of the peribiliary plexus might contribute to the development of ITBL is provided in a study by Moench et al.[24] These investigators have shown that additional flushing of the peribiliary plexus by controlled arterial backtable pressure perfusion is associated with a considerable reduction in ITBL after preservation with UW solution.[24] Apart from this, a proper harvesting technique of the liver and the extrahepatic bile duct is critically important to preserve the viability and vasculature of the bile duct. Although never studied in a clinical trial, it is accepted by every surgeon that the extrahepatic bile duct should be left covered with as much tissue as possible. Stripping of the bile duct should be avoided in order not to injure the microcirculatory blood supply.

Warm ischemic Injury

Two periods of warm ischemia can be distinguished during the transplant procedure. The first warm ischemia time (WIT), during harvesting and before cold preservation, and the second WIT, during graft implantation and before complete reperfusion. The first WIT, especially, is a major concern in grafts from nonheart-beating (NHB) donors. Several studies have shown that liver grafts from NHB donors are at increased risk of developing ITBL.[25–27] Concern exists that increased harvesting time, extending the first WIT, in addition to subsequent CIT and ischemia-reperfusion injury, may result in damage to the biliary epithelium.[25] Despite this plausible reasoning, no direct clinical evidence has directly linked prolonged harvesting time with ITBL, and the literature concerning this item is not conclusive.[25–29]

To reduce the incidence of ITBL, attempts have been made to reduce the second WIT. During revascularization of the graft, the most common technique is initial reperfusion via the portal vein, with subsequent reconstruction and reperfusion of the hepatic artery. Bile ducts, solely dependent on the hepatic artery for their blood supply, are exposed to warm ischemia during reperfusion via the portal vein alone. This situation has been hypothesized to increase damage of the biliary epithelium. To overcome this potentially harmful situation, Sankary et al.[18] have studied the impact of simultaneous versus sequential reperfusion of the portal vein and hepatic artery on the incidence of ITBL. These investigators observed a significant reduction of ITBL when livers were reperfused simultaneously via the portal vein and hepatic artery.[18] However, in a more recent study, we were not able to demonstrate a favorable effect of simultaneous arterial and portal reperfusion on the incidence of ITBL.[30]

In an attempt to reduce the second WIT further, some investigators have introduced retrograde perfusion of the liver graft via the inferior vena cava, after completing its anastomosis and during construction of the portal vein anastomosis.[31] Although this technique certainly results in an earlier reperfusion of the graft, the central venous blood that it is reperfused with has a lower oxygen pressure than the portal or arterial blood. In a randomized controlled clinical trial, Heidenhain et al.[32] have recently observed a higher incidence of ITBL in livers that were reperfused in a retrograde fashion, compared to antegrade reperfusion via the portal vein. The low perfusion pressure obtained during retrograde perfusion via the caval anastomosis may be an explanation for this. This low venous pressure may result in poor flushout and reperfusion of the peribiliary plexus, causing more ischemic biliary injury (J. Langrehr, personal communication, 2005).

Immunological injury

Several studies have provided evidence for an immunological component in the pathogenesis of ITBL.[15,17,33] ITBL has been associated with various immunologically mediated processes, such as ABO-incompatible liver transplantation, pre-existing diseases with a presumed autoimmune component (such as primary sclerosing cholangitis [PSC] and autoimmune hepatitis [AIH]), cytomegalovirus (CMV) infection, chronic rejection, and finally, with genetic polymorphism of chemokines.

ABO incompatibility

ABO blood type-mismatched liver transplantation has long been recognized to give rise to multiple complications.[5,34] The incidence of ITBL in ABO-incompatible OLT varies from 20% to 82%.[15] An explanation for this could be the fact that the antigens of the blood-type system are not only expressed on the vascular endothelium but also on biliary epithelial cells, making them a target for preformed ABO blood group antibodies.[5,15] Because of this high rate of complications and reduced graft survival rates, transplantation across the ABO border is nowadays discouraged.

Association with pre-existing disease

It has been well described in several studies that patients who are transplanted for PSC have a higher inci-

dence of ITBL after transplantation.[13,14,17,35.36] The association between ITBL and AIH has only been described recently.[17] PSC and AIH share a similar genetic predisposition to autoimmunity.[17] Taken together, these findings strengthen the hypothesis that ITBL may have an underlying (auto) immune component.

Cytomegalovirus

In patients suffering from acquired immunodeficiency syndrome (AIDS), infection with CMV has been shown to contribute to biliary problems, such as cholangitis.[37] After OLT, CMV infection has been associated with an increased incidence of anastomotic strictures and biliary leaks.[38] CMV inclusions have been demonstrated histopathologically in the extrahepatic bile duct specimen from a liver transplant patient who developed a biliary stricture during CMV infection.[38,39] A clear association between CMV and ITBL, however, has never been demonstrated.[17] In a recent large study of 1714 liver transplant recipients, Heidenhain et al.[40] could not find a higher incidence of ITBL in patients who had suffered from CMV infection versus those who had not. The role of CMV infection in the pathogenesis of ITBL, therefore, remains unclear.

Chronic rejection

Chronic rejection has been implicated as a potential cause of biliary strictures.[12,41,42] This effect is thought to be modulated not via direct injury to the biliary epithelium, but rather, via the arteriopathy accompanying chronic rejection, leading to narrowing of the medium-sized arteries. The resulting ischemia of the bile duct wall seems to play an important role in the loss of small bile ducts.[15,43,44] Although chronic rejection has been identified as a risk factor for the development of ITBL in several series,[15,20,41,45] this could not always be confirmed by others.[13,46] Therefore, the role of chronic rejection in the pathogenesis of ITBL remains to be elucidated.

Chemokines

Chemokines play a key role in postoperative immunomodulation, especially during rejection, as well as in postischemic injury. Evidence for a role of chemokines in the pathogenesis of ITBL after OLT has been provided by a genetic association study focusing on CC-chemokine receptor 5 (CCR5). CCR5 is a receptor for CC-chemokine ligand (CCL) 3 (macrophage inflammatory protein 1 alpha) and CCL4 (macrophage inflammatory protein 1 beta), which are overexpressed in infiltrating leukocytes.[47] Biliary epithelial cells have been shown to produce CC-chemokines that may bind specifically to CCR5.[48] *CCR5Δ32* polymorphism is a nonfunctional mutant allele of *CCR5*, with an internal deletion of 32 base pairs. A study of this polymorphism showed no differences in patient survival, rejection rates, retransplantation rates, or survival in OLT patients with *CCR5Δ32* compared with patients with wild-type *CCR5*.[49] Interestingly however, Moench et al.[33] recently found a very strong association between the presence of the *CCR5Δ32* polymorphism in recipients and the development of ITBL after OLT. These findings add to the existing evidence that immunological factors play a role in the pathogenesis of ITBL.

Bile-salt-induced injury

Another potential factor in the pathogenesis of bile duct injury after liver transplantation is bile-salt toxicity. Bile salts have potent detergent properties towards cellular membranes of hepatocytes and biliary epithelial cells. Normally, the toxic effects of bile salts are prevented by complex (mixed micelle) formation with phospholipids.

Evidence for a pivotal role of bile-salt-mediated hepatotoxicity in the pathogenesis of ischemia/reperfusion injury of liver grafts, has gradually emerged during the past decade. Using experiments in pigs, Hertl et al.[50] have shown that bile salts can seriously amplify preservation injury of the biliary epithelium. When porcine livers are flushed at the time of procurement with saline containing hydrophobic bile salts, the intrahepatic bile ducts are more seriously injured after even short periods of ischemia, compared to control livers which are flushed with saline.[50–52] Injury of the biliary tree can be prevented when an infusion of hydrophilic, instead of hydrophobic, bile salts is given to the donor animals prior to liver procurement.[50] Moreover, it has been demonstrated that the morphological characteristics of human common bile ducts are significantly altered when livers are perfused with UW solution mixed with gallbladder bile, compared to livers which are preserved with normal UW solution.[53] Of interest, we recently found that microscopic bile duct injury occurring early after human liver transplantation correlated with the formation of toxic bile, characterized by a high bile salt/phospholipid ratio.[54] Whether an increased bile salt/phospholipid ratio contributes to hepatic injury or whether it is an epiphenomenon, however, could not be identified in this clinical study. Therefore, we recently initiated a study, using a model of arterialized liver transplantation in mice that were heterozygous for the disruption of the gene encoding for the transporter of phospholipids into the bile, the *Mdr2* gene (multidrug resistance protein 2).[55] These mice disclose approximately half of the normal phospholipid concentration in bile, leading to an abnormally high bile salt/phospholipid ratio, but have a normal liver histology under normal conditions. When *Mdr2*+/– livers were

transplanted, after a short period of cold storage, into wild-type recipients, serious biliary injury developed. These findings provide evidence that endogenous bile salts act synergistically with ischemia/reperfusion in the origin of bile duct injury in vivo. In addition, these data indicate that intrahepatic cholestasis and intracellular bile salt retention may be critical mechanisms triggering hepatobiliary injury after liver transplantation. Even when the primary insult occurs to the bile ducts, hepatocellular injury is an invariable feature of cholestasis, associated with the accumulation of bile salts in the liver and blood.[56]

Current evidence indicates that bile-salt retention is a key early event that contributes to hepatocellular and biliary injury after OLT. Until more specific strategies become available, great care should be taken to avoid the exposure of bile duct epithelium to toxic bile salts during cold storage. Careful retrograde flushing of the bile ducts with preservation solution is therefore considered to be critical to remove residual bile salts. Furthermore, the extrahepatic bile duct should not be ligated during organ procurement, in order to ensure the flushout of bile and bile salts during organ procurement and cold storage.

Clinical presentation

The clinical presentation of ITBL is often not specific; symptoms may include fever, abdominal complaints, and cholestatis on liver function tests. In many patients, asymptomatic elevation of serum gamma glutamyl transferase and/or alkaline phosphatase is the first sign of biliary complications, prompting the initiation of further examinations, such as cholangiography.[16] Most patients with ITBL present with symptoms within the first 6 months after OLT.[7,12,13,17,57]

Diagnostic workup

The appropriate diagnostic workup has been discussed in several recent reviews.[58–60] Direct visualization of the bile ducts by endoscopic retrograde cholangiopancreaticography (ERCP), percutaneous transhepatic cholangiodrainage (PTCD) or drain-cholangiography remains the gold standard for making the diagnosis of ITBL.[7,12,13,17,24,61] Magnetic resonance cholangiopancreaticography (MRCP) is becoming increasingly important as a diagnostic test, with high positive and negative predictive values.[62–64] Cholangiographic imaging can show mucosal irregularities, narrowing of the lumen, and ductal dilatations.[65] A classification of ITBL has been proposed based on the localization of the abnormalities, distinguishing type I (extrahepatic lesions), type II (intrahepatic lesions), and type III (intra- and extrahepatic alterations).[66,67] However, this classification has not been widely accepted and used. In all cases of nonanastomotic biliary strictures, patency of the hepatic artery should be carefully studied and confirmed before the diagnosis of ITBL can be made.

The presence of ITBL can be suggested by biliary abnormalities in a liver biopsy, such as ductular proliferation and cholestasis.[13] However, ITBL remains a macroscopic and not a microscopic entity. No studies have been conducted correlating histological abnormalities in liver biopsies and the presence of ITBL.

Treatment

More than in any other biliary complication, treatment of ITBL has to be individualized. Direct treatment of strictures should be attempted via endoscopy or percutaneous dilatations and stenting. With prolonged and intensive endoscopic or radiological treatment, over 50% of patients can be treated successfully,[7,12,17,20,68,69] with some centers even reporting success in over 70%.[70] In many other patients, retransplantation may at least be postponed by using this strategy. Success will depend mainly on the severity of the strictures and their localization, with extrahepatic strictures responding better to therapy. In patients with successful radiological treatment, liver test results may improve, but they often remain disturbed.[14,69] Many physicians will provide medical treatment with ursodeoxycholic acid to their patients in order to improve bile flow and to obtain a more favorable composition of the bile.[68,71,72] However, the efficacy of this strategy in influencing the incidence or outcome of ITBL has never been properly evaluated in a randomized controlled clinical trial.

If nonoperative techniques are unsuccessful, surgery may be appropriate in selected patients. Especially when lesions are predominantly present at the level of the bile duct bifurcation, resection of the extrahepatic bile ducts and Roux-en-Y hepaticojejunostomy should be considered. Schlitt et al.[73] have reported clinical and biochemical improvement in 14 out of 16 patients with hilar ITBL who were treated by a hepaticojejunostomy or portoenterostomy. If all other treatment options have failed, retransplantation may be the only therapy left. Especially in the presence of secondary biliary cirrhosis, recurrent cholangitis, or progressive cholestasis due to extensive intrahepatic ITBL, retransplantation is mostly unavoidable.

The presence of ITBL is associated with a marked decrease in graft survival. Ultimately, up to 50% of patients with ITBL either die or need a retransplantation; however, mortality rates differ markedly among studies.[12,15,17]

Conclusion

Since the introduction of liver transplantation, biliary drainage has formed the so-called "Achilles heel" of this procedure. Early studies have reported disabling complications of the biliary tract in over 30% of the patients.[74] Fortunately, much has changed during the past decades. Liver transplantation is, nowadays, a standard treatment for patients with endstage liver disease, and survival is excellent, with 1-year patient survival rates of 80% to 90%. Multiple improvements in patient selection and perioperative management, as well as changes in surgical technique, have contributed to the success of OLT today. Unfortunately, despite these important improvements and enormous gains in experience, biliary complications can still be regarded as the "Achilles heel". The most incomprehensible type of biliary complications is ITBL. Although several risk factors for ITBL have been identified in recent years, the direct cause of ITBL can often not be identified in an individual patient. Although it is most likely that the pathogenesis of ITBL is multifactorial, several studies have strongly suggested a critical role for ischemic injury of the peribiliary vascular plexus. In addition, studies have provided evidence for the involvement of immunological processes, as well as bile-salt-induced injury of the biliary epithelium. Despite the important progress that has been made in the understanding of the pathogenesis of ITBL, the actual cause remains unidentified in many patients suffering from this troublesome complication after OLT. Therefore, more research will be needed in this area to better identify and understand the mechanism of ITBL. Only in this way, more specific preventive and therapeutic strategies can be developed, which may further improve patient and graft survival after OLT.

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