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TOPIC HIGHLIGHT

2015 Advances in Liver Transplantation

Management of biliary complications after liver transplantation

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Abstract

Biliary complications (BC) currently represent a major source of morbidity after liver transplantation. Although refinements in surgical technique and medical therapy have had a positive influence on the reduction of post-operative morbidity, BC affect 5% to 25% of trans-planted patients. Bile leak and anastomotic strictures represent the most common complications. Nowadays, a multidisciplinary approach is required to manage such complications in order to prevent liver failure and retransplantation.

Key words: Biliary complication; Bile leak; Anastomotic stricture; Endoscopic treatment; Liver transplantation

Core tip: Biliary complications (BC) represent the downside of liver transplantation, impacting postoperative morbidity as well as patient and graft survival. In this paper, we will analyze the most common BC, along with diagnosis, management and treatment modalities.

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INTRODUCTION

Liver transplantation (LT) is the standard of care for

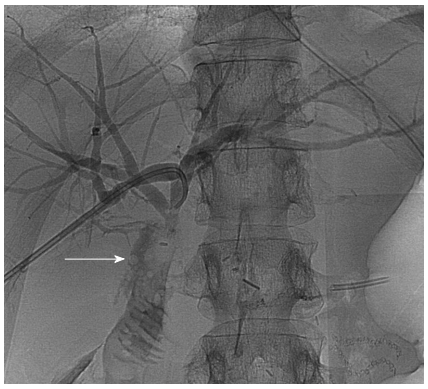

Figure 1 Biliary fistula post hepatojejunostomy.

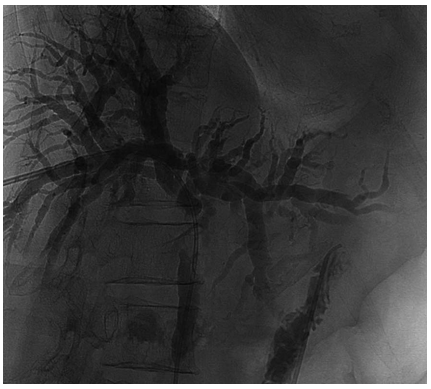

Figure 2 Ischemic anastomotic stricture after duct-to-duct anastomosis.

end-stage liver disease. Although LT can currently be considered as a consolidate procedure and various refinements in surgical techniques are required, organ preservation and immunosuppressive management have reduced complications and contribute to better outcomes[1], biliary complications (BC) remain the main downside of this procedure, affecting 5% to 25% of transplanted patients[2]. The most common causes of BC are bile leakage, anastomotic and non-anastomotic strictures, and bile duct obstruction. According to the literature[3-8], the main risk factors are technical complications, ischemia/reperfusion injury, ABO mismatch, hepatic artery complications (thrombosis and stenosis), donor age and cytomegalovirus infection. The aim of this article is to review and focus on the treatment of BC after LT.

Surgical technique

Two different types of biliary anastomoses can be performed in LT: Duct-to-duct (DD) and hepatojejunostomy (HJ). Different factors determine the choice of biliary reconstruction. In most cases, a DD anastomosis is preferred (90% of deceased donor LT[9,10] and 60% in living donor LT[11] due to its simpler technical feasibility, preserved function of Oddi's sphincter, and endoscopic access preservation. In the literature, two kinds of DD anastomoses have been described: End-to-end and side-to-side. Davidson *et al*[12] have described an equal effectiveness of both reconstructions. HJ is preferred in case of size disparity between donor and recipient bile duct, recipient diseased duct or previous transplant or biliary surgery. In addition to the type of reconstruction, no evidence has been demonstrated regarding the suturing method (interrupted or continuous[13]) or materials. However, an inadequate surgical technique can be responsible for BC[14]. A T tube was routinely used after DD anastomosis to reduce the incidence of BC. Most retrospective studies cannot conclude in favor of the use of a T tube[15], and some of them point towards a potential negative effect[16-18] on anastomosis. Recently, a meta-analysis[19] including six prospective randomized trials demonstrated no benefit in terms of T tube, and consequently it could not be recommended.

Diagnosis

The onset modality of BCs varied. In the presence of pain, abnormal liver function tests, increased levels of inflammatory markers, fever, and bilious secretion in the abdominal drain, further radiological examinations were necessary. In case of ongoing clinical suspicion, cholangiography remains the gold standard for the exploration of BCs. In the presence of a T tube, a simple cholangiography could reveal the origin of BCs. If a T tube is not used, endoscopic retrograde cholangiopancreatography (ERCP) is the method of choice in case of DD anastomosis. In case of HJ anastomosis, percutaneous transhepatic cholangiography is the first-line diagnostic exam. Recently, magnetic resonance cholangiopancreatography has guaranteed a good sensitivity and specificity in order to prevent invasive exploration. Ultrasonography may be helpful to detect the presence of biloma, biliary tree dilatation, and to explore all vascular anastomoses by means of a Doppler examination. Further procedures such as liver biopsy could be necessary in case of suspected graft dysfunction.

Types of BC

BC can be divided into several categories which are anastomotic leak (Figure 1), biliary strictures (Figure 2), non-anastomotic strictures (Figure 3), and biliary obstruction (stones, sludge and cast). Each complication usually occurs in different postoperative periods and requires different management options.

Anastomotic leaks: Bile leaks occur in 5% to 10% of deceased donor LT[20] and in 10% to 15% of living donor LT[21]. They can occur during the anastomosis, at T tube insertion, on the cystic duct stump and on the cut surface in case of partial graft. Early postoperative leak can be identified. They usually occur within one month after LT. Late bile leaks[22] rarely occur. In the early postoperative period, bile leak can originate directly from the anastomosis, and it is most likely due to technical problems or insufficient arterial bile duct vascularization. Other rare causes of bile leak are due to an incorrect suture of the cystic duct stump

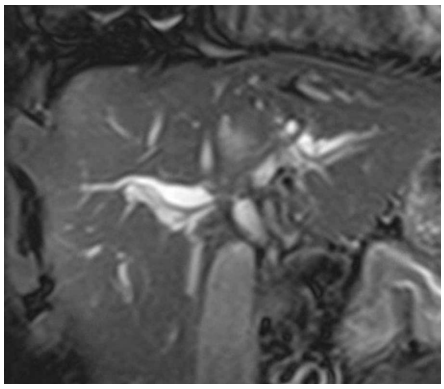

Figure 3 Non anastomotic stricture six months post liver transplantation.

and may originate from the resection surface in case of living donor or split liver. In particular, caudate lobe biliary branches, which usually drain in the left liver are sometimes drained in the right liver, increasing the risk of leak either in donors or recipients[20,23]. Late bile leaks are related to T tube[24] removal in nearly 1% of cases, with a fistula arising directly from the insertion site. In some cases, especially in case of early accidental T tube removal, a biliary peritonitis can occur, due to the incomplete T tube tract scarring.

Biliary strictures: As described in the literature, biliary strictures represent a complication which can occur in 13% in deceased donor LT and in 19% in in living donor LT[9]. Biliary strictures can be divided into two categories, *i.e.*, anastomotic strictures and non-anastomotic strictures. The main cause responsible for anastomotic strictures can be inadequate anastomoses, usually occurring in the early postoperative period and inflammatory strictures due to ischemic events or biliary fistulas. The mechanism of non-anastomotic strictures remains unclear, but it is often related to ischemic events. Non-anastomotic strictures are present in the entire biliary tree, especially in the hilum. Non-anastomotic strictures, also called ischemic cholangiopathies, can be caused by long-lasting cold ischemia times[25]. Generally, biliary strictures are considered as late complications, occurring within 6 mo[26,27] after LT, even though some cases may occur later, especially when associated with ischemic cholangitis for arterial thrombosis[28] or immunologic disorders[29].

Other complications: Bile leaks and anastomotic strictures represent the main BC. Liver test perturbation may be due to other causes. Outflow bile duct obstruction can be caused by Oddi's sphincter dysfunction, as described in about 2% to 7% of patients[30]. It is often associated with a stump denervation of the recipient bile duct or with a chronic sphincter inflammation. Other causes of bile duct dilatation can be stones, sludge or cast. The formation of stones is often due to an underlying stenosis which induces an increased bile viscosity, occurring in 3% to 12% of cases[31]. Sludge is like a mixture of particles precipitated from the bile, often composed of cholesterol and calcium salt which generates a progressive bile duct lumen obstruction in 2% of cases[32]. Damage (ischemia, rejection, infection, obstruction) of the biliary tree mucosa can provoke a cast syndrome, defined as the presence of cast (desquamated epithelial cells mixed with bile products) within the intrahepatic and extrahepatic biliary system. Its incidence varies from 3% to 18% in the literature[33]. Mucoceles, an uncommon complication after LT occurring in 2% of patients[34], are defined as a collection of mucus present in the remnant cystic duct. This abnormal dilatation can cause extrinsic compression on the bile duct.

MANAGEMENT

Bile leaks

Even if its role is still debated[35], the T tube can be a useful tool for a rapid diagnosis of bile leak in case of early postoperative bile leak. A T tube cholangiogram could be used diagnostically and a simple drainage through the tube opening could be therapeutic, preventing any invasive treatment. Without the use of a T tube, endoscopic treatment is the standard of care[22,36,37]. A simple sphincterotomy could be therapeutic in case of small bile leak[38]. An endoscopic stent could be necessary for major bile leaks, with a short-term removal[27] of the prosthesis in case of successful treatment. In case of HJ anastomosis, in case of endoscopic treatment failure (even if expert teams substantiate the use of double-balloon enteroscopy[39]), transhepatic percutaneous[40] treatment becomes an alternative. Although percutaneous transanastomotic internal-external drainage guarantees good postoperative results, it is technically difficult due to the absence of leak-induced bile duct dilatation. Re-operation and re-transplantation[9] for bile leak, although described in the literature, become increasingly anecdotal due to improvements in radiology and endoscopy.

Biliary strictures

Biliary strictures are usually classified into anastomotic strictures and non-anastomotic strictures. Anastomotic strictures usually involve the anastomotic site whereas non-anastomotic strictures could be multiple and present either in the hilum and in the intrahepatic portion of the bile duct, with a guarded prognosis as compared to anastomotic strictures[41]. Concerning anastomotic strictures, the treatment aims to dilate the stenotic segment. Considering the access route, endoscopy is preferred to the percutaneous approach[42] due to a reduced morbidity, better efficacy, and increased comfort for the patient[43]. Endoscopic treatment, performed *via* ERCP, consists of sphincterotomy and several sessions of dilatation followed by placement of a plastic stent. Some studies compared simple balloon dilatation to balloon dilatation and simultaneous plastic stent placement, showing a lower recurrence rate and requiring fewer sessions in combined treatment[44,45]. The success rate of treatment is approximately 75%[45,46]. Multiple

sessions are usually performed bimonthly and could be necessary to obtain satisfying results[47,48]. The necessity of a repetitive approach, entailed the increased use of metallic stents, which can achieve a higher diameter and develop less obstruction as compared to plastic stents. This concept is theoretically correct but has not found practical evidence neither with the use of partially nor fully covered stents as compared to plastic stents[41]. The percutaneous approach, mostly used in case of HJ anastomosis, guarantees goods results in terms of success and recurrence rates[29]. In case of endoscopic/percutaneous treatment failure, surgery represents a valid treatment alternative, considering the effect of prolonged biliary obstruction on liver function. Surgical revision was necessary in 10% to 20% of cases with anastomotic stricture[29].

Early arterial thrombosis represents the main risk factor for non-anastomotic strictures. Thrombosis associated with the absence of arterial collateral perfusion (otherwise present in late arterial thrombosis) is strongly associated with non-anastomotic strictures in 50% of cases[14]. Early detection could well reduce the rate of retransplantation[28], requiring a rapid revascularization in order to prevent graft loss. Ischemic-type lesions are difficult to manage, especially in case of multiple intrahepatic strictures. Medical treatment can be attempted, even if not evidence-based, with the use of ursodesoxicolic acid to increase bile flow and reduce lithogenicity. Considering the frequent association with cholangitis, a large use of antibiotic therapy and prophylaxis is often necessary[49]. Endoscopic treatment with multiple stent placement for non-anastomotic strictures usually requires long-term stenting, and despite encouraging results described in the literature[48,49], 30% to 50% of patients undergo re-transplantation[22,27,49] due to the progressive onset of liver dysfunction caused by chronic biliary cirrhosis. An immunomediate mechanism is responsible for late (> 1 year) non-anastomotic strictures[50,51], requiring the same management of ischemia-mediated strictures.

Other complications

Most other pathological conditions are related to a difficult bile duct emptying. On radiological findings, they can be identified as common bile duct filling defects. Different causes contribute to this dysfunction, arising from the presence of stones, sludge, cast syndrome or cystic duct mucoceles[52]. Most of these complications are treated using an endoscopic approach, consisting of sphincterotomy and ERCP with balloon dilatation and basket extraction. In case of endoscopic treatment failure, surgery represents a valid alternative.

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