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EDITORIAL

Biliary complications following liver transplantation

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Abstract

Biliary tract complications are the most common complications after liver transplantation. These complications are encountered more commonly as a result of increased number of liver transplantations and the prolonged survival of transplant patients. Biliary complications remain a major source of morbidity in liver transplant patients, with an incidence of 5%-32%. Post liver transplantation biliary complications include strictures (anastomotic and non-anastomotic), leaks, stones, sphincter of Oddi dysfunction, and recurrence of primary biliary disease such as primary sclerosing cholangitis and primary biliary cirrhosis. The risk of occurrence of a specific biliary complication is related to the type of biliary reconstruction performed at the time of liver transplantation. In this article we seek to review the major biliary complications and their relation to the type of biliary reconstruction performed at the time of liver tranplantation.

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Key words: Liver transplantation; Complication; Biliary; Stricture; Leak; Endoscopic retrograde cholangiopancreatography

Core tip: Biliary complications continue to be a major cause of morbidity in liver transplant recipients. In this article, we review the etiology, as well as the main types of biliary complications according to the technique of biliary reconstruction and liver transplant procedure performed. Their management is also discussed with endoscopic techniques emerging as the preferred treatment option, obviating the need for surgery in majority of patients.

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INTRODUCTION

Since the first experiences with liver transplantation in the 1960s, this procedure has become a standard treatment for end stage liver disease. Limited primarily by the donor liver supply, the number of orthotopic liver transplants (OLT) has continued to increase. In the United States alone, according to the American Liver Foundation, 6500 liver transplantations were performed in 2005. Although, because of constant improvements in surgical techniques, the rate of biliary complications following liver transplantation has been decreasing; they remain a major source of morbidity and mortality[1,2]. Post liver transplantation biliary complications include strictures, leaks, stones or debris, and sphincter of Oddi dysfunction (SOD). T-tube biliary reconstruction, Roux-en-Y anastomosis, ischemia, reperfusion injury, hepatic artery thrombosis (HAT), cytomegalovirus infection, and primary sclerosing cholangitis are some of the risk factors that have been implicated in biliary complications.

TYPES OF BILIARY RECONSTRUCTION

The choice of biliary anastomosis is a major determinant of the risk of biliary complications after OLT[3,4]. The two most common forms of biliary reconstruction are choledochocholedochostomy (CC, duct-to-duct anastomosis) and choledochojejunostomy (CJ, connection of the bile duct to a portion of jejunum). The choice of biliary reconstruction is determined by multiple factors, including the underlying liver pathology, the size of donor and recipient bile ducts, prior transplant or previous biliary surgery, and the preference of the performing surgeon. There are no clear-cut guidelines on the optimal type of biliary reconstruction, and considerable variability exists between surgeons.

CC is the most common biliary reconstruction procedure performed during OLT. This type of reconstruction is usually preferred because the procedure is technically easier, it preserves the function of Sphincter of Oddi, and it also allows easy endoscopic access to the biliary system after the surgery[5]. Furthermore, the preservation of the sphincter of Oddi, theoretically decreases the risk of ascending cholangitis as it serves as a barrier against the reflux of enteric contents into the biliary tree. CC can be performed either with or without a T-tube. Routine use of a T-tube allows direct measurement of bile output and color in the early post-operative period, maintains easy access for radiological evaluation of the biliary system and allows rapid decompression of the biliary tree if needed. It also may reduce the risk of anastomotic stricture formation. On the other hand, the use of T-tubes has been associated with bile leak and cholangitis at the time of their removal. A recent retrospective study of 180 patients demonstrated an increased rate of overall complications (33% *vs* 15.5%) and an increased rate of cholangitis (10% *vs* 2.2%) in patients with a T-tube compared to those without. In that study patients without a T-tube had an increased survival rate compared to the T-tube population (80.1% *vs* 72.8%), an observation that was attributed to higher complication rates among those with a T-tube[5]. This observation is supported by a recent meta-analysis consisting of 1027 patients, in which those without a T tube had a decreased incidence of cholangitis and peritonitis with overall decreased rate of biliary complications. Interestingly, this meta-analysis did not show any significant differences between the T-tube and non T-tube groups in terms of other complications such as anastomotic bile leaks, fistulas, choledochojejunostomy revisions, stenting of the bile duct, hepatic artery thromboses, retransplantation, and mortality due to biliary complications[6].

CJ is another type of biliary reconstruction usually recommended in patients with pre-existing biliary disease such as primary sclerosing cholangitis, or prior biliary surgery, and also when there is a size mismatch between donor and recipient ducts. Compared to CC, CJ takes longer to perform and adversely affects the ability to perform an endoscopic evaluation of the biliary system after the liver transplantation. Potential complications of CJ include intestinal perforation, stricture, leakage, and bleeding at jejuno-jejunostomy site.

DIAGNOSIS OF BILIARY COMPLICATIONS

The presentation of biliary complications varies considerably. Some complications such as bile leaks may occur immediately in the post-operative period, while others may take weeks to develop. The clinical presentation can vary from asymptomatic patient with moderate liver enzyme elevations to a septic patient with fever and hypotension due to ascending cholangitis. Whenever a biliary complication is suspected, work-up usually begins with laboratory evaluation and an abdominal doppler ultrasound. Abdominal ultrasounds are relatively inexpensive, and are easy to perform. An abdominal ultrasound allows for the evaluation of the biliary tree and the corresponding hepatic vasculature. The positive predictive value of abdominal ultrasound is very high, especially in the presence of dilated bile ducts. In the absence of dilated bile ducts, the sensitivity of the ultrasound for detecting biliary obstruction ranges from 38%-68%[7]. In the event that the ultrasound does not reveal evidence of bile duct dilatation despite clinical suspicion, the next step can be magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP), depending on their availability. MRCP has excellent sensitivity (93%-100%) in detecting biliary strictures; and can also offer a road map for the endoscopist in planning the necessary intervention[8]. Another advantage of MRCP is that it does not carry the invasive risk involved with ERCP or other interventions such as percutaneous transhepatic cholangiography (PTC). The upside of ERCP and PTC, on the other hand, is that they both offer a potential therapeutic advantage over MRCP. It should be noted, however, that ERCP is associated with a high failure rate in patients with Roux-en-Y reconstruction, except when double balloon enteroscopy is available to assess the biliary tree. PTC is usually reserved in cases where ERCP cannot be performed.

Bile leaks after OLT

Bile leaks, along with strictures, account for the majority of complications post-OLT. Bile leaks occur in 2%-25% of cases after liver transplantation and can be classified in two categories: early bile leaks, which present within 4 wk of OLT; and late bile leaks, which present beyond this time[9-12].

Etiology: Early bile leaks usually occur at the anastomotic site or at the T-tube insertion site. They can be caused by ischemia, relative downstream obstruction, sphincter of Oddi hypertension, or as a result of T-tube removal[13]. The majority of bile leaks after OLT are associated with either planned or inadvertent T-tube removal, and the leak often occurs at the T-tube insertion site. One factor that has been shown to predict development of bile leak after T-tube removal is the presence of mucosal duct irregularities on cholangiography.

Presentation: The presentation varies with extent of the leak. Bile leak should be suspected in any patient who develops abdominal pain, fever or any sign of peritonitis after liver transplant, especially after T-tube removal. Bile leaks not related to T-tube removal typically present within the first 30 d after OLT. Some patients, especially those on corticosteroids, may be asymptomatic, with no signs of pain or fever. In such cases, any unexplained elevations in serum bilirubin, fluctuation in cyclosporine levels, or bilious ascites should raise suspicion for a bile leak.

Management: Once the clinical suspicion of a bile leak following T-tube removal is raised, initial management usually involves pain control with analgesics, intravenous fluids, and supportive care. Biliary leaks due to ischemia are difficult to treat since the cause is usually not corrected by endoscopic or radiologic intervention. Leaks due to other causes usually respond to non-operative diversion of biliary flow, such as unclamping of the T tube, endoscopic sphincterotomy with or without endoscopic stenting at the time of ERCP, or placement of a PTC. ERCP with stenting of the bile duct, sphincterotomy, nasobiliary drainage, or a combination of these techniques has been shown to have high rates of success[9,14]. Most studies report resolution of symptoms in 85%-100% of the cases[15]. Although one study reported better results with nasobiliary drainage; most centers use an internal biliary stent to overcome the difference in pressure in the bile duct and the gut. The stent usually remains in place for several weeks. PTC is commonly used in cases where ERCP cannot be performed, or in patients with Roux-en-Y reconstruction where the biliary orifice cannot be reached with a regular sideview endoscope. In rare cases, surgical intervention may become necessary[9].

Biliary strictures

Post liver transplantation biliary strictures are usually classified as anastomotic or non-anastomotic. The incidence of biliary stricture ranges from 5%-15% after deceased donor liver transplantation and 28%-32% after living donor liver transplantation[7]. Strictures are commonly seen as late complications, occurring approximately 5-8 mo after transplantation.

Anastomotic strictures

Anastomotic strictures (AS) at the site of biliary anastomosis are frequent after OLT and can occur in both CC and CJ type of reconstruction. AS are more common after CJ than CC due to the direct bilioenteric connection[1,12].

Etiology: The pathogenesis of AS is believed to be from inadequate mucosa-to-mucosa anastomosis, surgical technique, local tissue ischemia, and the fibrotic nature of the healing process[16]. Early bile leak is also considered to be a risk factor for developing AS[9]. In those with a T-tube, strictures at the CC anastomosis are often not typically evident until after removal of the T-tube. A slight and transient narrowing of the biliary lumen occurs frequently in biliary anastomosis shortly after the OLT due to post-operative edema. It is uncertain how many of these cases progress to clinically significant strictures.

Presentation: Biliary stricture should be suspected in any OLT patient who presents with jaundice, fever, abdominal pain, or even in patients with asymptomatic biochemical cholestasis. Dilatation of the bile ducts proximal to the biliary anastomosis may be observed on imaging studies in some patients but is not a pre-requisite for diagnosis. Histologic findings may be suggestive of biliary obstruction, such as pericholangitis or bile duct proliferation.

Management: When a clinically significant AS is found, treatment is warranted. In recent years, ERCP has seen an increase in popularity in the management of AS. Although results differ markedly, studies have demonstrated good response after endoscopic therapy in over 75% of the patients[17,18]. Endoscopic treatment is thus regarded as the treatment of choice for AS, especially in the CC group of patients. Stenting of the stricture during ERCP is performed with or without balloon dilatation of the stricture. The initial stent is then exchanged for a larger stent or multiple stents every 3 mo for an average of 1 year to dilate the stricture and prevent clogging and stone formation. In patients with CJ reconstruction, the initial treatment usually involves stenting by percutaneous approach. Some centers have reported that early strictures respond better to therapy than late strictures. If a stricture does not respond to endoscopic or percutaneous therapy, surgery may be indicated. Previous endoscopic or percutaneous treatment has not shown to influence the success rate of surgery in treating such complications.

Non anastomotic strictures

Non anastomotic strictures (NAS), also known as ischemic type strictures, are well known and have been described since the beginning of liver transplantation. They are frequently hilar in location, but can also be diffusely intrahepatic. NAS tend to be longer and multiple on presentation. NAS incidence ranges from 5%-15% with mean time to presentation of 3.3-5.9 mo post-OLT[19,20].

Etiology: A few theories have been proposed for the development of NAS. The blood supply to the supraduodenal bile duct is predominantly from vessels which are resected during OLT. The remaining blood supply to the donor bile duct then comes from the hepatic artery and its branches, which are tenuous and highly susceptible to ischemic injury. In patients with NAS, up to 50% have demonstrable HAT[21]. Prolonged cold ischemia time has also been shown to be responsible for the development of NAS. Besides ischemia, an immunological cause has also been proposed. This is mainly due to the observa-

tion of an increased incidence of NAS in cases with ABO-incompatible grafts, in patients with autoimmune hepatitis or primary sclerosing cholangitis, in patients suffering from chronic ductopenic rejection, and those with a CC chemokine receptor 5delta32 polymorphism. In many cases, NAS are probably multifactorial in origin with injury resulting from one or more of the above mechanisms[7,22].

Management: The presentation of NAS is similar to that of AS. NAS are more difficult to manage than AS, as treatment in each case has to be individualized. It is therefore difficult to make generalized recommendations for management of NAS. In cases with early HAT, aggressive management with either revascularization or early re-transplantation has been recommended. In NAS not associated with HAT, endoscopic or percutaneous therapy are often attempted first. Repeated dilatation with stenting seems to be the most accepted treatment form[14]. Treatment success depends upon stricture severity, number, and location. Extra-hepatic strictures generally respond better to therapy. Different studies report variable treatment success rates, ranging from 50%-70%[10,23]. If radiological and endoscopic therapies fail, surgery may become necessary. Success rates are higher if surgery is done within 2 years of OLT and if the liver biopsy does not show any significant fibrosis. Retransplantation may also be considered in patients with treatment failure, or in the presence of secondary biliary cirrhosis, recurrent cholangitis, or progressive cholestasis.

SOD

Another common occurrence after OLT is a mild increase in the size of donor and recipient common bile ducts. In certain cases, significant dilatation of both recipient and donor bile duct in association with biochemical abnormalities occurs in the absence of cholangiographic evidence of obstruction. In these cases, SOD is suspected. The incidence of SOD is reported to be up to 7%[11,24].

Etiology: The pathogenesis of SOD is attributed to denervation of the sphincter during OLT. This leads to an increase in basal pressure, thus causing increased pressures in the choledochal duct[24]. Very few studies have directly assessed the pressures in the sphincter of Oddi post-OLT. Two types of SOD have been proposed on the basis of pathogenic mechanisms: stenosis and dyskinesia[16,25,26]. Any process that leads to chronic inflammation and fibrosis, can lead to sphincter stenosis. Dyskinesia, on the other hand, is usually seen as a result of functional disturbance of the sphincter.

Management: There have been virtually no clinical trials that demonstrate the best treatment option for SOD. In recent years, endoscopic therapy with sphincterotomy with or without stenting has been the most acceptable treatment option for SOD.

Biliary stones, sludge, and casts

On ERCP, stones, sludge and casts are usually seen as a defect in the contrast column and described as "filling defects". Intrinsic bile duct obstruction, in the form of biliary stones and sludge, can virtually occur at any time following the OLT. Sludge is described as a thick collection of mucous, calcium bicarbonate and cholesterol cystals, which, when left untreated, can go on to form biliary stones. Sludge and casts usually occur within the first year of transplant, while stones tend to occur later on.

Etiology: Theoretically, anything that increases the viscosity of bile or reducing flow can predispose to the formation of sludge, and stones. Bile duct mucosal damage due to obstruction, ischemia, or infection is thought to play a role in the development of casts. Of patients presenting with biliary stones and sludge, most will have an underlying stricture. In addition, medications such as cyclosporine may play a role in bile lithogenicity by inhibiting bile secretion and promoting functional biliary stasis. Bile in transplant patients has been shown to be supersaturated with cholesterol, which is aggravated by T-tube drainage and depletion of the bile acid pool.

Presentation: Patients commonly present with abdominal pain, cholestatic liver tests, and uncommonly with cholangitis.

Management: A study demonstrated that cholangiography is the only reliable imaging method for sludge; ultrasonography and CT scans are of limited value. If sludge alone is present, then it would be reasonable to first attempt medical treatment with ursodeoxycholic acid. Endoscopic therapy with sphincterotomy, lithotripsy and stone extraction are successful in treating majority of filling defects, especially biliary stones[23].

Biloma

Bile rupture and spilling of bile within the liver and abdominal cavity may result in the formation of a biloma. Small bilomas, especially ones that communicate with the biliary tree, may resolve on their own. Although bilomas can generally be treated with antibiotics and percutaneous drainage, some may require placement of a biliary stent in the extrahepatic bile duct[9]. Surgical drainage of a biloma is viewed as a last resort option.

Hemobilia

One of the rare complications seen after OLT is hemobilia. It is usually associated with percutaneous liver biopsy or PTC. The commonly described triad of right upper quadrant pain, jaundice, and gastrointestinal bleed is seen only in a minority of patients. Treatment of hemobilia requires both hemostasis and treatment of any associated biliary obstruction by clots. The bleeding stops spontaneously with supportive therapy and correction of coagulopathy in some cases. Embolization of the

bleeding vessel by interventional radiology is required if bleeding is persistent or severe[27]. Removal of clots from the biliary tree for relief of obstruction is usually done by ERCP.

Ductopenia

Ductopenia (also referred to as bile duct paucity and vanishing bile duct syndrome) is a descriptive term for small intrahepatic bile duct loss from any cause. In post liver transplantation patients, acute and chronic rejection and ischemia are the most common culprits. The diagnosis is established by liver biopsy in the appropriate clinical setting. Treatment depends mainly on the underlying etiology of ductopenia.

CONCLUSION

Biliary complications following liver transplantation are relatively common and continue to be a challenging aspect in the management of such patients. The development of these complications is heavily influenced by the type of anastomosis during surgery. The majority of biliary complications after liver transplantation are now a days being managed endoscopically rather than surgically. ERCP, in particular, has proven to be relatively safe and effective in the management of these complications.

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