Post-liver Transplant Biliary Complications

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Biliary tract complications remain a common source of morbidity and mortality in liver transplant (LT) recipients with an estimated incidence of 5–30% after orthotopic LT and a mortality rate of up to 10%. Biliary complications after LT may be related to various factors including hepatic artery thrombosis or stenosis, ischemia reperfusion injury, immunologic injury, infections, donor pool, and technical issues which include imperfect anastomosis and T-tube-related complications. Management of the detected biliary complications includes nonsurgical and surgical methods. A majority of these post transplant biliary complications can be treated with endoscopic retrograde cholangiography. If unsuccessful, a percutaneous intervention or surgery may be required. In this article, we review the incidence, clinical presentation, and management of the main types of biliary complications. (J CLIN EXP HEPATOL 2012;2:81–85)

The overall incidence of biliary complications after orthotopic liver transplant (LT) has been reported to be 5–30%.^{1,2} The incidence of biliary complications is greatest in the first few months after transplantation with the frequency decreasing after the first post-transplantation year.³ Biliary complications include anastomotic strictures (AS), non-anastomotic bile duct stricture (NAS), stone formation, bile leak, biloma, biliary necrosis, sphincter of Oddi dysfunction (SOD), cholangitis, hemobilia, recurrent malignancy, and post-transplantation lymphoproliferative disorder. The etiology of biliary complications is multifactorial. Major risk factors include variations in the biliary tract anatomy, size of reconstructed bile duct(s) (BD), ischemic damage to BD (hepatic artery complication, warm and cold ischemia time, BD blood supply), method of biliary reconstruction (type, suture methods, suture material, stent or T-tube use), immunologic issues (ABO-incompatibility), and infection (biliary sepsis, cytomegalovirus [CMV]) (Table 1).⁴ They can be classified as early or late based on whether they occur within 3 months or >3 months after transplantation. Bile leaks are most common in the early postoperative period, whereas biliary strictures, biliary stones, and SOD occur later.^{1,5} At least two-thirds of biliary complications are diagnosed within 3 months after transplantation.¹ The improved patient survival is attributable to the progress in advances in

pre-operative patient selection, organ procurement, improved surgical techniques, new endoscopy, and percutaneous radiologic interventional modalities.³ Management of post-LT biliary tract complications should be a team effort of endoscopists, transplant surgeons, and radiologists.

DIAGNOSIS OF BILIARY COMPLICATIONS

The clinical presentation of post transplantation complications varies from an asymptomatic patient with abnormal liver function tests to another presenting with fever, liver failure, abdominal pain, or septicemia. Bile duct stricture, leak, and obstructions are the most frequent complications. Patients with bile leaks usually present with increasing abdominal distension or pain in the perioperative period or after the removal of T-tube. Asymptomatic cholestasis is usually the presenting feature of biliary stricture. Some patients with concomitant biliary stones may present with cholangitis.

Postoperative Doppler ultrasound (US) is the main initial imaging modality for the evaluation of post-transplant complications due to its easy availability and high sensitivity and specificity in the detection of vascular and biliary complications (Figure 1). It is important to rule out hepatic thrombosis or stenosis, as it is frequently associated with biliary complications. Doppler US has a lower sensitivity (38–68%) for detecting biliary obstruction in

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Abbreviations: AS: anastomotic strictures; ERCP: endoscopic retrograde cholangiopancreatography; MRCP: magnetic resonance cholangiopancreatography; NAS: non-anastomotic strictures; PTC: percutaneous transhepatic cholangiography; SOD: sphincter of Oddi dysfunction
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Table 1 Risk factors for development of biliary complications.

T-tube biliary reconstruction
Ischemia-reperfusion injury
Hepatic artery thrombosis
Cytomegalovirus infection
Primary sclerosing cholangitis
Split liver grafts
Right-lobe liver donor transplantation

Figure 1 Algorithm for the diagnosis and management of biliary complications.

CT: computed tomography, D-D: Duct-to-duct, D-R: Duct-to-Roux loop, ERCP: endoscopic retrograde cholangiopancreatography, MR: magnetic resonance, MRCP: magnetic resonance cholangiopancreatography, PTC: percutaneous transhepatic cholangiopancreatography.

the absence of biliary dilatation.⁶ It may also not be able to help differentiate bile leaks from nonbiliary postoperative fluid collections such as ascites, abscess, and hematoma, but it can help detect a localized biloma.⁷ In patients in whom no flow or nonvisualization of the hepatic artery is identified by Doppler US, computed tomography (CT) angiography or magnetic resonance angiography is indicated. If suspicion of a biliary complication is high and Doppler US is inconclusive, knowledge about the duct-to-duct (D-D) anastomosis is important to determine further appropriate imaging. If there is a T-tube in situ, T-tube cholangiography is preferable to magnetic resonance cholangiopancreatography (MRCP) because the distention of the BDs with contrast material permits better stricture analysis and functional assessment.⁷ If there is no T-tube, MRCP is preferred for the evaluation of BD dilatation and obstruction and avoids the complications associated with invasive percutaneous transhepatic cholangiopancreatography (PTC) or endoscopic retrograde cholangiopancreatography (ERCP) (Figure 1). However, the main disadvantage of MRCP is the lack of its therapeutic ability and high cost. The MRCP was shown to have a sensitivity of 95%, a positive predictive value of 98%, and an overall accuracy of 95% compared with ERCP as the reference standard.⁸ Usually, complications following choledochocholedochal anastomosis are managed with ERCP, whereas complications following Roux-en-Y choledochojejunal anastomosis often require PTC.⁹ Cholescintigraphy is a good non-invasive alternative for the evaluation of bile leaks but not biliary strictures. Patients with abnormal liver blood test and negative abdominal US and MRCP should undergo a liver biopsy to evaluate for rejection as the primary pathology.

Biliary Leaks

Biliary leaks remain a significant source of morbidity in patients undergoing LT, with an incidence ranging from 2% to 21%.¹⁰ Bile leakage can be categorized into anastomotic

and non-anastomotic in site. The most common site for clinically important leakage is the biliary anastomosis (D-D or biliary-enteric).^{1,11} Anastomotic leaks are mainly related to errors in surgical techniques and/or ischemic necrosis at the end of the BD and usually occur early in the postoperative period.^{2,6} Non-anastomotic leaks could occur from the T-tube exit site or tract, cystic duct stump, duct of Lushka or damaged accessory BDs or from the cut surface of the graft in living donor living transplant.^{1,2,6,12} Bile leakage after transplantation has been considered as a significant risk factor for subsequent development of AS.^{6,13,14} Bile leaks are most common in the early postoperative period (before 1 month from the LT), as the majority are related to technical issues, insufficient arterial supply to the biliary anastomosis secondary to vascular complications, active bleeding from cut ends of BDs, denuding the BDs during harvesting, or excessive tension on ductal anastomosis.⁶ There is no association between an increase in the rate of bile leaks with the method of biliary reconstruction. Late postoperative BD leaks (after 1 month from the LT) are frequently related to elective or inadvertent removal of the T-tube, with an incidence of 7% with a mean time to presentation of 118 days after transplantation despite prolonged T-tube placement.¹⁵ Diagnosis is suggested in a patient who develops persistent abdominal pain or peritoneal signs after T-tube removal. A hepatobiliary iminodiacetic acid scan (HIDA) has a reasonable accuracy in non-invasive detection of a bile leak. The ERCP is considered the gold standard for the diagnosis of bile leaks and also offers excellent therapeutic results. It involves sphincterotomy and placement of a biliary stent for about 2–3 months. This can treat over 90% of biliary tract leaks.^{1,6,16} If the leak is small, it can be managed with sphincterotomy alone. Other treatment options for bile leak, if ERCP is not feasible, include PTC-guided drainage or surgical reconstruction. Ischemic biliary leaks are difficult to treat with endoscopic or radiologic intervention and generally require surgical reconstruction.

Figure 2 Cholangiograms showing (A) high-grade anastomotic stricture, (B) balloon dilation, and (C) stent placement.

Biliary Strictures

Biliary strictures occur in around 2–12% of patients after LT. They are more common in living donor LT (LDLT) than in deceased donor LT (DDLT) and more common in non-heart-beating donor livers than in brain-stem dead donor livers. Biliary strictures can present at any time after transplantation, but the incidence is greatest in the first 5–8 months.¹⁷ Biliary strictures can be classified as anastomotic and non-anastomotic depending on the location.^{1,2}

Anastomotic Strictures

Incidence of AS is around 5–10% of transplanted patients.¹ Anastomotic stricture is usually isolated, short in length, and resulted from fibrotic changes within the first year after transplantation.^{1,14} Anastomotic stricture that appear early in the postoperative period are usually related to surgical technical issues, and may include improper techniques, small diameter of the BDs, size mismatch between the donor and recipient BDs, tension at the anastomosis, excessive use of electrocauterization for control of BD bleeding, infection, and bile leakage.^{18,19} Whereas later onset AS is most likely to indicate fibrotic healing changes due to ischemia either of donor or recipient BD.¹⁴ Treatment of AS is managed with ERCP, as it is diagnostic and therapeutic. During ERCP, the stricture is traversed with a guide

wire and balloon dilation of the stricture is performed followed by placement of plastic biliary stent(s) (Figure 2). Usually, several sessions of ERCP (every 2–3 months) with dilation and stent exchange are required. Long-term response in patients with AS after ERCP is in the range of 70–100% in DDLT.²⁰ Placement of covered self-expanding metal stent in patients with treatment failure or recurrence of stricture after balloon dilation and plastic stent placement is being studied.

Non-anastomotic Strictures

Non-anastomotic strictures account for 10–25% of all stricture complications, with an incidence between 0.5% and 9.6%. It comprises an array of biliary abnormalities with different pathogenesis and variations in anatomical localization and severity, ranging from slight, localized mucosal irregularity to extensive and diffuse biliary strictures.¹⁴ The NAS can be further classified into three categories: macroangiopathic, microangiopathic, and immunogenic causes.²¹ Macroangiopathic causes of NAS result from arterial insufficiency like hepatic artery thrombosis. Microangiopathic causes include prolonged cold and warm ischemia time, delayed re-arterialization of graft or transplants from non-heart-beating donors which result in ischemia reperfusion injury to the biliary epithelium. Immunologically related injuries to the biliary epithelium

or vascular epithelium result from chronic rejection, ABO-incompatibility, CMV infection, or recurrent primary sclerosing cholangitis (PSC). Approximately one-fifth of the patients with PSC develop recurrent disease in the graft. Microangiopathic causes-related strictures are often multiple, longer, proximal to the anastomosis in the extra- or intrahepatic BDs and occur earlier than AS with a mean time to stricture development of 3.3–5.9 months.^{20,22} Ischemic NAS usually presents within 1 year post transplantation, whereas NAS presenting later nearly always result from immunologic causes.²¹

Non-anastomotic strictures secondary to early hepatic artery thrombosis usually requires urgent revascularization or re-transplantation, whereas NAS due to late hepatic artery thrombosis or any other causes is treated with endoscopy.²³ Endoscopic therapy of NAS is considered as first line in management; however, it is less successful than that in AS. The endoscopic approach is similar to that in AS and comprises extraction of the biliary sludge and casts, balloon dilation of all accessible strictures, and placement of plastic stents, which are replaced every 3 months for an average of 1 year. It is reported that only 50–75% of patients with DDLT had a long-term response to endoscopic therapy and the median time of response was 185 days.^{6,16,20} Patients with a persistent stenosis despite adequate balloon dilatation and stenting require surgical revision and reconstruction. Use of self-expandable metallic stents in patients with refractory stenosis is also being studied. The NAS are more difficult to treat with more complications and less favorable overall outcomes including increased graft loss and death and up to 50% of patients will require liver re-transplantation.²¹

Biliary Stones, Sludge, and Casts

The incidence of biliary stones after LT is 3.3–12.3%.^{24–27} Post-transplant calculi and sludge formation are most likely the result of mechanical obstruction mainly strictures, bacterial infection,^{6,24} ischemia, biliary reflux, and biliary mucosal inflammation. The ERCP with sphincterotomy is very successful in removing 90–100% of stones or debris in almost all cases.^{6,16,24,25} Theories as to the etiology of biliary casts include sloughed biliary epithelium due to prolonged cold storage time or transient or ongoing ischemia, chronic rejection, infection, bile stasis, and alteration of the bile milieu.¹⁶ Biliary cast syndrome describes the cholangiographic findings of multiple fixed filling defects in the intrahepatic or extrahepatic biliary tree that conform to the luminal dimensions of the segment of BD. It typically occurs within the first year after transplant. Treatment of biliary casts is more challenging, sometimes requiring various procedures like sphincterotomy, ball and basket extraction, stent placement, lithotripsy, and PTC.¹³ Surgery may be required if endoscopic methods are not successful. Up to 22% of patients with biliary cast syndrome will require re-transplantation.²⁸

Sphincter of Oddi Dysfunction

Also termed ampullary dysfunction occurs in as many as 5% of patients following LT.²⁶ The cause in the post transplant setting is poorly understood but is possibly related to operative denervation of the ampullary region of the native duct, resulting in abnormal ampullary relaxation and increased intraductal biliary pressure.^{1,6,16,29} It is usually suspected clinically by persistently elevated liver enzymes in a cholestatic pattern, improvements in liver function tests with T-tube unclamping or cholangiography showing dilation of the native BD to a diameter >10 mm and delayed drainage of contrast medium (>15 min) without evidence of an anatomic cause for biliary obstruction.^{1,6,16,29} Thuluvath et al⁶ reported CMV and other opportunistic infections that may also play a pathologic role in post-transplant SOD. Hepatobiliary scintigraphy and sphincter or T-tube manometry are used as diagnostic modalities. Endoscopic sphincterotomy and/or biliary stenting are usually a successful treatment.¹

Biloma

Bilomas are defined as localized intrahepatic or parahepatic fluid collections that may be caused by anastomotic dehiscence secondary to ischemia. Limited data exist regarding the incidence of biloma after LT. Post-transplantation biloma should be suspected in patients with fever or abdominal pain or abnormalities of hepatic enzymes, as it is a major infectious complication of LT. They are seen as discrete, rounded, hypo-echoic in ultrasonography or hypo-attenuating fluid collections in CT.⁷ Bilomas communicating with the biliary tree may resolve spontaneously or may require endoscopic stent placement. Noncommunicating bilomas are usually treated with antibiotics and percutaneous drainage.²¹

Complications of Endoscopic Therapy in Post-liver-transplant Patients

The complication rate of ERCP in post-LT patients is comparable with other population. Complications including pancreatitis, post-sphincterotomy bleeding, infection, or perforation may occur in up to 10% of patients.^{16,30} Endoscopic management in LDLT recipients may be difficult due to the complex nature of the D-D reconstruction. SOD in general population is a well-known risk factor for post-ERCP. However, in transplant patients, this risk is probably less.

CONCLUSION

Biliary complications are common source of morbidity after LT. Although the incidence has dramatically decreased in the past few years, biliary stricture and leakage continue to be a source of significant morbidity; therefore high index of suspicion is needed for prompt intervention.

Management of the detected biliary complications includes nonsurgical and surgical methods. The ERCP is effective in the management of strictures and obstruction due to stones or sludge and for SOD. Surgical approach is required if endoscopic approach is not feasible or successful.

CONFLICTS OF INTEREST

All authors have none to declare.

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