Intrahepatic biliary strictures after liver transplantation

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Abstract
Biliary complication has been one of the most common complications after liver transplantation. Nonanastomotic strictures and dilatations involving the intrahepatic biliary tree have been recognized as biliary complications. These lesions were reported to be associated with hepatic artery thrombosis; prolonged preservation time; ABO-incompatible organs; and immunological injury, including injuries to vascular endothelial cells (chronic rejection) and the bile duct (primary sclerosing cholangitis). However, the etiology of these lesions appeared to be mostly related to ischemic injury. Anatomical research on the arterial supply of the bile duct has provided further insights into bile duct blood supply and its surgical implications. The biliary tract is supplied with arterial blood by a vasculature called the peribiliary vascular plexus. Any injury to the peribiliary vascular plexus may contribute to ischemic death of the biliary system mucosa. At many points, the process of liver transplantation exposes the endothelial cells and peribiliary vascular plexus to ischemic injury. The majority of intrahepatic biliary strictures (IHBS) are diffuse or bilateral. A percutaneous or an endoscopic approach has been used as the initial treatment. However, a low threshold for surgical intervention (retransplantation) should be adopted, because these patients demonstrate high mortality. The aim of this article is to review the anatomy, etiology, clinical picture, diagnosis, management, and prognosis of IHBS after liver transplantation.

Keywords Biliary complication · Intrahepatic biliary stricture · Liver transplantation · Hepatic artery thrombosis

Introduction
Biliary complication has been one of the most common complications after liver transplantation.¹⁻⁵ The incidence of biliary complications has been reported to be 22%–64%.⁶ Nonanastomotic strictures and dilatations involving the intra-hepatic biliary tree have been recognized as biliary complications.⁷ These complications have been reported as diffuse biliary strictures,⁷ ischemic-type biliary strictures,⁸ ischemic cholangitis,⁹ intra-hepatic biliary strictures (IHBS),¹⁰¹¹ and nonanastomotic strictures.¹² These lesions were reported to be associated with hepatic artery thrombosis; prolonged preservation time; ABO-incompatible organs; and immunological injury, including injuries to vascular endothelial cells (chronic rejection) and the bile duct (primary sclerosing cholangitis).⁷⁻¹² However, the etiology of these lesions appeared to be mostly related to ischemic injury. Anatomical research on the arterial supply of the bile duct has been performed recently.¹³⁻¹⁷ These studies have provided further insights into the bile duct blood supply and its surgical implications. Embryological studies of the developing biliary system in humans have been performed.¹⁸¹⁹ Several hypotheses have been proposed regarding the development of the biliary tree. The extrahepatic bile duct develops from the cystic diverticulum, while the intrahepatic bile duct develops through the ductal plate from the hepatic diverticulum. The ductal plate undergoes remodeling and is shaped into the intrahepatic biliary system. The microstructure of the development of the normal and pathologic biliary tract has been reported including a study of the blood supply.²⁰

The aim of this article is to review the anatomy, etiology, clinical picture, diagnosis, management, and prognosis of IHBS after liver transplantation. We also focus our attention on the ischemic nature of the pathogenesis of IHBS.

Blood supply of the bile duct
Anatomical studies of the blood supply of the bile duct have been performed using microscopic examination of
vascular plexus. Study of the blood supply of the right hepatic bile duct showed that 60% of the blood supply of the bile duct came through arteries from below the duct, including the retrograde arterial supply of the right hepatic bile duct and gastroduodenal artery. Thirty-eight percent of the blood supply of the bile duct came from through arteries from above the duct, including the right hepatic artery, cystic artery, and left hepatic artery. The remaining 2% of the blood supply of the bile duct came from the common hepatic artery. The arterial supply of the superduodenal duct was shown to be axial, with 3 o’clock and 9 o’clock arteries (a 12 o’clock artery can also exist). The great variability of the arterial supply of the bile duct is recognized. The bile duct is not only a duct but also has peribiliary glands. The biliary tract is supplied with arterial blood by a vasculature called the peribiliary vascular plexus. Study of the blood supply of the right and left hepatic ducts showed that the peribiliary vascular plexus around the right and left hepatic duct was continuous with a similar plexus surrounding the common bile duct and common hepatic duct. The peribiliary vascular plexus has a three-layer pattern (inner, intermediate, and outer layers) in the large intrahepatic bile ducts. The peribiliary vascular plexus around the interlobular bile ducts and bile ductules consists of scattered capillaries with no layer formation. One of the most important functions of the hepatic artery is the nourishment of the bile ducts. Venous drainage from the plexus goes into the portal veins.

Development of the human biliary system

Several hypotheses have been proposed regarding the development of the biliary tree. However, new information about the developing human biliary system at the porta hepatitis has been reported recently. The extrahepatic bile duct develops from the cystic diverticulum, while the intrahepatic bile duct develops through the ductal plate from the hepatic diverticulum. The ductal plate undergoes remodeling and is shaped into the intrahepatic biliary system, with the mesenchyme playing an important role in this remodeling process. There is no solid stage during the development of the biliary system. Thus, no joining up of the extra- and intrahepatic system is required. The intrahepatic biliary system is in luminal continuity with the extrahepatic bile duct throughout gestation. Some parts of the ductal plate are eliminated and others are transformed into the biliary system.

Etiology of IHBS

Nonanastomotic strictures and dilatations involving the intrahepatic biliary tree have been recognized as biliary complications after liver transplantation. These complications have been reported as diffuse biliary strictures, ischemic-type biliary strictures, ischemic cholangitis, intra-hepatic biliary strictures, and non-anastomotic strictures. These lesions were reported to be associated with hepatic artery thrombosis: non-heart-beating donors; prolonged preservation time; cadaveric donors with cardiac arrest; ABO-incompatible organs; and immunological injury, including injuries to vascular endothelial cells (chronic rejection) and the bile duct (primary sclerosing cholangitis). However, the etiology of these lesions appeared to be mostly related to ischemic injury. On many occasions, the process of liver transplantation exposes the endothelial cells to injury. Cold preservation injury, reperfusion injury, and immunological injury can happen in the course of liver transplantation. These endothelial injuries may cause hepatic arteriolar arteriopathy, vasoconstriction, and microvascular thrombosis. The great variability of the arterial supply of the bile duct is recognized. The biliary tract is supplied with arterial blood by a vasculature called the peribiliary vascular plexus. Any injury to the peribiliary vascular plexus may contribute to the ischemic death of the biliary system mucosa. Hepatic artery thrombosis (HAT) after liver transplantation is the most typical clinical scenario which causes IHBS. However, we have recognized many patients with IHBS without HAT. The IHBS injuries to the bile duct typically occur in a diffuse or bilateral proximal fashion. They may occur at any point after liver transplantation. Any injuries to the peribiliary vascular plexus may cause these biliary strictures. It seems clear that IHBS is a sequel of ischemic injury to the peribiliary vascular plexus caused by various factors. Lymphoma, epithelioid hemangioendothelioma, hepatocellular carcinoma, recurrent cholangiocarcinoma, and recurrent primary sclerosing cholangitis have also been reported as etiologies of IHBS.

Clinical picture of IHBS

IHBS can occur at any point after liver transplantation. Elevations of liver enzymes, bilirubin, and canalicul enzymes (cholangitis picture) are common. We experienced early IHBS in a recipient of a cadaveric liver graft from a non-heart-beating donor. Early IHBS may be related to donor factors, including an unstable donor, a donor with cardiac arrest, prolonged preservation time, and a non-heart-beating donor. However, IHBS may also occur in the absence of any risk factors. We experienced a patient with diffuse IHBS 2 weeks after liver transplantation, without any specific causes (Fig. 1). In this patient, the donor was young, the cold ischemic time was 8h, and the hepatic artery was patent. The