

Co-occurrence of Nonanastomotic Biliary Stricture and Acute Cellular Rejection in Liver Transplant

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Abstract

Background: Nonanastomotic biliary stricture is generally considered the most troublesome biliary complication after liver transplant. Nonanastomotic biliary stricture owing to immunologic cholangiopathy (such as acute cellular rejection) has not been reported. We describe 2 patients with the co-occurrence of nonanastomotic biliary stricture and acute cellular rejection after pediatric live-donor liver transplant.

Case 1: A 13-month-old male infant with liver cirrhosis underwent an ABO-identical live-donor liver transplant using a left lateral segment graft. Eighty days after the live-donor liver transplant, fever with liver dysfunction and dilatation of the intrahepatic bile duct occurred. Percutaneous transhepatic biliary drainage and a liver biopsy were performed. The histopathologic evaluation indicated the presence of acute cellular rejection. After percutaneous transhepatic biliary drainage and steroid pulse treatment, the patient showed good clinical outcome.

Case 2: A 21-month-old female infant with biliary atresia underwent an ABO-identical live-donor liver transplant using a left lateral segment graft. Twenty-six days after the live-donor liver transplant, percutaneous transhepatic biliary drainage for B3 and a liver biopsy were performed, owing to fever, with liver dysfunction, and dilatation of the intrahepatic bile duct. Histopathologic evaluation indicated the presence

of acute cellular rejection. After percutaneous transhepatic biliary drainage and steroid pulse treatment, the patient showed good clinical outcome.

Conclusions: It is important for patients with nonanastomotic biliary stricture to undergo early liver biopsy because the nonanastomotic biliary stricture may be coincident with, or caused by, acute cellular rejection.

Key words: Nonanastomotic biliary stricture, Acute cellular rejection, Liver transplant, Percutaneous transhepatic biliary drainage, Liver biopsy

Biliary complications have long been recognized as a major cause of morbidity and graft liver failure in patients after liver transplant (LT).¹ Biliary stricture is often referred to as *anastomotic* or *nonanastomotic*, and nonanastomotic biliary stricture is generally considered to be the most troublesome type. The reported incidence of nonanastomotic biliary stricture varies greatly between different series, ranging from 1.4% to 19.0%.²⁻⁶ The most common causes of nonanastomotic biliary stricture are related to hepatic artery thrombosis⁷; nonanastomotic biliary stricture without hepatic artery thrombosis is rare.^{3, 8} Other identified causes include (1) ischemic injury (such as prolonged cold or warm ischemia time),⁹ severe reperfusion injury,¹⁰ or deceased-donor LT¹¹; (2) immunologic injury such as chronic rejection,¹² ABO incompatibility,¹³ cytomegalovirus infection,¹⁴ or recurrence of primary disease (primary sclerosing cholangitis or autoimmune hepatitis)¹⁵; and (3) bile-salt-induced injury.¹⁶ However, nonanastomotic biliary stricture owing to immunologic cholangiopathy such as acute cellular rejection has not been reported after LT.

Herein, we describe 2 children with co-occurrence of nonanastomotic biliary stricture and

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acute cellular rejection after pediatric live-donor liver transplant (LDLT).

Case Reports

Case 1

A 13-month-old male child with liver cirrhosis of unknown cause underwent an ABO-identical LDLT using a left lateral segment graft because of recurrent cholangitis. The graft volume to standard liver volume was 85.1%. Although the operative time was 12 hours 33 minutes, and the bleeding volume was 250 mL, the intraoperative course had no major problems that possibility could have led to ischemic injury. The cold and warm ischemia times were 0 hours 50 minutes and 1 hour 2 minutes. For biliary reconstruction, a Roux-en-Y hepaticojejunostomy using a lost stent was used for a single-orifice bile duct 5 mm in diameter. Tacrolimus and methylprednisolone were used as standard postoperative immunosuppression. The postoperative course was uneventful, except for an episode of steroid-resistant acute cellular rejection requiring muromonab-CD3 treatment. The patient was discharged from the hospital 32 days after the LDLT. There was no hepatic artery thrombosis, *cytomegalovirus* infection, or recurrence of the primary disease.

However, 80 days after the LDLT, a fever with liver dysfunction and dilatation of the intrahepatic bile duct occurred, and the patient was readmitted. Because cholangitis was refractory to conservative treatment, percutaneous transhepatic biliary drainage was done. During percutaneous transhepatic cholangiography, all of the peripheral intrahepatic bile duct was found to be dilated multifocally at the level of the identified region and did not show any signs of anastomotic biliary stricture (Figure 1). At the same time, a percutaneous transhepatic liver biopsy was performed, and this indicated the presence of acute cellular rejection (Figure 2). Methylprednisolone was administered at 20 mg/kg for 3 days and thereafter, gradually tapered the dosage by halving it on each consecutive day. After percutaneous transhepatic biliary drainage and steroid pulse treatment, the patient had a stable clinical course. It was not necessary to perform balloon dilatation, and the percutaneous transhepatic biliary drainage tube was removed 9 months after percutaneous transhepatic biliary drainage. The patient is currently doing well 3 years after the LDLT.



Figure 1. Percutaneous transhepatic cholangiography showed that all of the peripheral intrahepatic bile ducts were dilated multifocally at the level of the identified region, and did not demonstrate any signs of anastomotic biliary stricture.

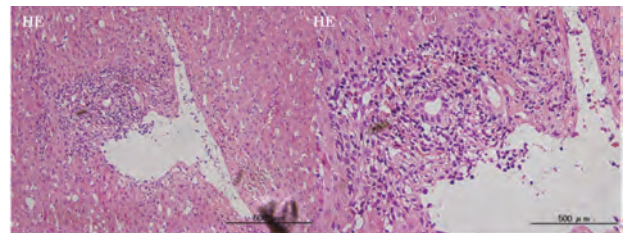


Figure 2. Histopathologic evaluation indicated the presence of acute cellular rejection and cholangitis. Portal inflammation was polymorphous, including eosinophils and lymphocytes ("rejection-type" infiltrates) (arrow). Bile duct inflammation included lymphocytes and/or neutrophils. The biopsy specimen also showed signs of endothelialitis, in which lymphocytes had attached themselves to the venous endothelium and then migrated beneath it, thus lifting it.

Case 2

A 21-month-old female child with biliary atresia underwent ABO-identical LDLT using a left lateral segment graft because of recurrent cholangitis. The graft volume to standard liver volume was 60.5%. Although the operative time was 9 hours 56 minutes, and the bleeding volume was 1069 mL, there were no intraoperative problems that could have led to ischemic injury. The cold and warm ischemia times were 2 hours 33 minutes and 0 hours 35 minutes. For biliary reconstruction, Roux-en-Y hepaticojejunostomies using a lost stent by a silicone drain (10-F BLAKE silicone drain, Johnson & Johnson, Tokyo, Japan) was performed for double-orifice bile ducts, which were 2 and 3 mm in diameter. Tacrolimus and methylprednisolone were used as standard postoperative immunosuppression.

There was no acute cellular rejection, hepatic artery thrombosis, or *cytomegalovirus* infection.

At 26 days after the LDLT, because of fever with liver dysfunction and dilatation of the intrahepatic bile duct, percutaneous transhepatic biliary drainage for B3 was done. During the percutaneous transhepatic cholangiography, the peripheral intrahepatic bile duct was found to be dilated unilaterally and focally, but did not show signs of anastomotic biliary stricture (Figure 3). However, because the patient's liver dysfunction had not improved, percutaneous transhepatic liver biopsy was performed 28 days after the LDLT. The histopathologic evaluation indicated the presence of acute cellular rejection (Figure 4). Methylprednisolone was administered at 20 mg/kg for 3 days and thereafter, tapered gradually by halving the dosage on each consecutive day. After percutaneous transhepatic biliary drainage and steroid pulse treatment, the patient showed a stable clinical course. The patient was discharged 93 days after the LDLT. It was necessary to perform balloon dilatation for a nonanastomotic biliary stricture, and the percutaneous transhepatic biliary drainage tube was removed 6 months after percutaneous transhepatic biliary drainage. Currently, the patient is doing well 2 years after the LDLT.



Figure 3. Percutaneous transhepatic cholangiography showed that the peripheral intrahepatic bile duct was dilated unilaterally and focally and did not demonstrate any signs of anastomotic biliary stricture.

Discussion

Liver transplant has become the criterion standard for patients with end-stage liver disease, but biliary

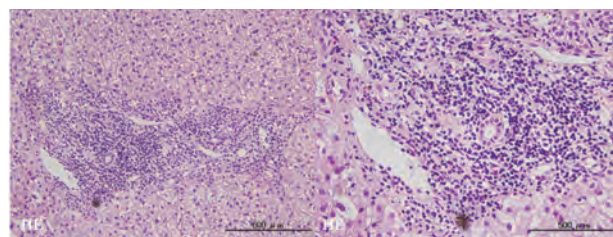


Figure 4. Histopathologic evaluation indicated the presence of acute cellular rejection and cholangitis. Portal inflammation was polymorphous, including eosinophils and lymphocytes ("rejection-type" infiltrates) (arrow). Bile duct inflammation included lymphocytes and/or neutrophils. The biopsy specimen also showed signs of endothelialitis, in which lymphocytes had attached themselves to the venous endothelium and then migrated beneath it, thus lifting it.

complications after LT remain, despite improvements and innovations in surgical techniques, occasionally leading to graft failure or death. Biliary stricture is often referred to as *anastomotic* or *nonanastomotic*, and nonanastomotic biliary stricture is generally thought to be the most troublesome type of biliary complication.¹ The most-common causes of nonanastomotic biliary stricture are related to hepatic artery thrombosis,⁷ and nonanastomotic biliary stricture without hepatic artery thrombosis is rare.^{3, 8} Although the pathogenesis of nonanastomotic biliary stricture is likely multifactorial, several studies have strongly suggested a critical role for ischemic injury of the peribiliary vascular plexus. In addition, studies have provided evidence for immunologic processes as well as bile-salt-induced injury of the biliary epithelium.⁸⁻¹⁶ Nonanastomotic biliary stricture owing to immunologic cholangiopathy (eg, acute cellular rejection) has not been reported. In such cases of concurrent nonanastomotic biliary stricture and acute cellular rejection, no instances of hepatic artery thrombosis, *cytomegalovirus* infection, recurrence of the primary disease, and reperfusion injury owing to prolonged warm ischemia time has been recorded. Therefore, ischemic injury of the peribiliary vascular plexus owing to acute cellular rejection-induced nonanastomotic biliary stricture may be responsible.

On the other hand, nonanastomotic biliary stricture may occur with acute cellular rejection by chance, because in such cases, it cannot be verified that nonanastomotic biliary stricture is caused by acute cellular rejection. However, in patients with co-occurrence of nonanastomotic biliary stricture and acute cellular rejection after LT, cholangitis and acute cellular rejection often coexist. It is necessary to

detect both nonanastomotic biliary stricture and acute cellular rejection to ensure adequate treatment, because nonanastomotic biliary stricture and acute cellular rejection occasionally lead to graft liver failure or can be fatal. Therefore, it is important for patients with nonanastomotic biliary stricture without hepatic artery thromboses to undergo an early liver biopsy to determine whether the acute cellular rejection is coincidental or causal.

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