Transplant Infectious Disease . ISSN 1398-2273

Case report

Successful treatment of recurrent cholangitis complicating liver transplantation by Roux-en-Y limb lengthening

D. Vrochides, S.A. Fischer, G. Soares, P.E. Morrissey. Successful treatment of recurrent cholangitis complicating liver transplantation by Roux-en-Y limb lengthening.
Transpl Infect Dis 2007. All rights reserved

Abstract: A 40-year-old male developed sepsis due to cholangitis. Five years earlier he underwent liver transplantation with hepaticojejunostomy. Over the past 18 months, he had 6 episodes of cholangitis. Radiologic studies demonstrated no biliary obstruction. Surgical intervention to eliminate bile reflux and stasis by lengthening the Roux-en-Y limb from 30 to 90 cm was curative. He has had no further episodes of cholangitis or hospitalization in the past 2 years. This case is the first description to our knowledge of a simple technique to treat recurrent cholangitis in patients with normal biliary anatomy, but inadequate biliary drainage following liver transplantation.

D. Vrochides[1], S.A. Fischer[2], G. Soares[3], P.E. Morrissey[1]

[1]Department of Surgery, Rhode Island Hospital, [2]Division of Infectious Diseases, [3]Diagnostic Imaging, Brown Medical School, Providence, Rhode Island, USA

Key words: cholangitis; liver transplantation; bile reflux; efferent loop; dysmotility; Roux-en-Y

Correspondence to:
Paul E. Morrissey, MD, FACS, Division of Organ Transplantation, Rhode Island Hospital, 593 Eddy Street, APC 921, Providence, RI 02903, USA.
Tel: 401 444 8345
E-mail: Pmorrissey@lifespan.org

Received 10 March 2006, revised 26 August, 2 November 2006, accepted for publication 14 November 2006

DOI: 10.1111/j.1399-3062.2007.00221.x
Transpl Infect Dis 2007

Cholangitis is a frequent complication in the early period following orthotopic liver transplantation (OLT); however, recurrent cholangitis, especially years after surgery, is rare in the absence of stricture or biliary obstruction. We describe a patient who developed multiple episodes of cholangitis several years after OLT with Roux-en-Y hepaticojejunostomy. Biliary obstruction was not present, but a short Roux-en-Y limb permitted chronic reflux into the hepatic ducts resulting in episodic infection. Lengthening the Roux-en-Y limb by reconstructing a more distal jejunojejunostomy was curative. This therapeutic strategy has not been previously reported in the transplantation literature.

Case report

A 40-year-old male recipient of a liver transplant with a history of multiple episodes of cholangitis and sepsis presented with fever, rigors, and abdominal pain. A few days earlier, the patient experienced low-grade fever and epigastric pain. He contacted his primary care physician and was started on ciprofloxacin for presumed cholangitis, having suffered multiple similar episodes. His condition worsened and he was admitted to the intensive care unit with a temperature of 39.1 °C, blood pressure 90/54 mmHg, and a pulse of 120 beats minute. The white blood cell (WBC) count was 6300/mm^3 and liver function studies demonstrated a bilirubin of 1.0 mg/dL, alkaline phosphatase 358 IU/L, and normal transaminase values. Cultures of the sputum and urine were negative, whereas cultures of the blood grew *Escherichia coli*. The organism was resistant to ampicillin, ampicillin/sulbactam, cefuroxime, and ciprofloxacin. His condition improved with intravenous imipenem/cilastatin. A surgical consultation was obtained because of the increasing frequency of these episodes of cholangitis.

The patient had a history of cirrhosis secondary to hepatitis B viral infection. Five years earlier he received a liver transplant. His immediate postoperative course was complicated by a common bile duct leak managed by conversion of the initial choledochocholedochostomy to a retrocolic hepaticojejunostomy. The initial immunosup-

Abbreviations: CT, computed axial tomography; ERCP, endoscopic retrograde cholangio-pancreatography; HBV, hepatitis B virus; OLT, orthotopic liver transplantation; PTC, percutaneous transhepatic cholangiography; WBC, white blood cell.

pression consisted of tacrolimus, azathioprine, and prednisone. The prednisone was tapered to low doses and eventually eliminated in the first year. Tacrolimus levels were maintained at 5–10 ng/mL.

Over the next 2 years, he experienced several febrile episodes presumed secondary to cholangitis. During the next 18 months (post-transplant months 21–38), he was admitted to 3 hospitals on 4 separate occasions with sudden onset of fever, rigors, and abdominal pain; blood cultures were performed on only one occasion and grew *E. coli*. In each instance, a diagnosis of cholangitis was established and the patient recovered with intravenous antibiotics (Table 1). Azathioprine was discontinued and the patient was maintained on tacrolimus monotherapy. Despite this reduction in immunosuppression, the patient continued to experience several episodes of presumed cholangitis that were managed as an outpatient with oral antibiotics. Repeatedly, he was placed on chronic suppressive oral antibiotic therapy with quinolones and/or amoxicillin/clavulanic acid, cycling every 1–3 months. In total, this patient had 12 documented episodes of fever and right upper quadrant pain beyond the first year following transplantation. Laboratory studies were often normal except for a transiently increased alkaline phosphatase; jaundice was absent. The majority of these episodes were attributed to cholangitis and treated with antibiotics. Bile cultures were not obtained.

One year before this admission the patient underwent an abdominal computed tomography (CT) scan, endoscopic retrograde cholangio-pancreatograpy (ERCP), and magnetic resonance cholangiopancreatography (MRCP). None of these tests revealed occult abscess or obstruction of the hepaticojejunostomy or the gastrointestinal tract. Between episodes, the patient was generally well and employed full time. Hepatitis B virus (HBV) DNA titers were undetectable and his allograft function was normal. Medications included tacrolimus, lamivudine, omeprazole, and insulin. He did not smoke, drink alcohol, or use illicit drugs.

A percutaneous transhepatic cholangiogram (PTC) performed during this admission (the first to our institution,

Representative febrile episodes and infectious work-up after transplantation

Time post transplant (months)	Symptoms	Temp °F (°C)	Alk phos (IU/L)	Blood cultures	Other studies	Treatment
10	Fever, abd pain, diarrhea	103 (39.45)	220	Not done		Levofloxacin alternating with amox/clav every month
20	Fever, abd pain	102.5 (39.2)	182	Not done		Amox/clav
24	Fever, myalgias, abd pain	102.9 (39.4)	90	Negative on antibiotics	CT negative, CSF negative	Zosyn, levofloxacin; alternating levofloxacin, amox/clav every 3 months
32	Fever, abd pain (outpatient)	103.1 (39.5)	134	Not done		Ciprofloxacin for 21 days
38	Fever, rigors, headache, abd pain	101 (38.34)	278	*Escherichia coli*	Ultrasound negative, colonoscopy negative, CT negative	Ciprofloxacin for 4 weeks; *E. coli* sensitive to quinolones
47	Fever, abd pain, emesis	102 (38.9)	79	Negative on antibiotics	Ultrasound negative, CT negative, colonoscopy negative	Ampicillin-sulbactam, levofloxacin
60	Fever, rigors, hypotension	104.6 (40.34)	170	*E. coli* (resistant to quinolones)	PTC negative, ERCP negative, MRCP negative	Imipenem; *E. coli* resistant to quinolones. (Initial presentation to Rhode Island Hospital)
61	Persistent fever on imipenem	101.2 (38.45)	258	Negative on antibiotics	Intraoperative cultures + for *Enterococcus*	Roux-en-Y revised; imipenem and vancomycin for 4 weeks
63	Fever, hypotension	102.8 (39.34)	226	*E. coli* (2 strains)	PTC negative	Roux-en-Y revised again; imipenem × 6 weeks

Temp, temperature; alk phos, alkaline phosphatase (normal range 40–130 IU/L); abd, abdominal; amox/clav, amoxicillin/clavulanate; CSF, cerebrospinal fluid; CT, computed tomography; ERCP, endoscopic retrograde cholangiogram; MRCP, magnetic resonance cholangiogram; PTC, percutaneous transhepatic cholangiogram.

Table 1

now 60 months after the OLT) demonstrated a normal biliary tree, absence of obstruction, and filling of the blind end of the Roux-en-Y loop. This non-functional portion of the Roux-en-Y loop measured 20 cm and showed delayed emptying consistent with stasis. We postulated that this configuration might produce bacterial overgrowth responsible for the cholangitis. The redundant limb was resected (Fig. 1) and the patient was discharged on the fifth postoperative day. Intraoperative cultures from the limb (performed on imipenem/cilastatin) revealed 1+ growth of *Enterococcus*.

Three months later, the patient was readmitted with *E. coli* sepsis due to cholangitis. The strain was identical to that in two previous admissions by susceptibility testing. The total bilirubin measured 3.4 mg/dL, alkaline phosphatase 806 IU/L, and the alanine transferase 134 IU/L on admission. One week later, the total bilirubin peaked at 9.2 mg/dL. A PTC revealed occlusion of both hepatic ducts and an external biliary drain was placed.

This drain was subsequently changed for an internal–external stent, which was advanced into the Roux-en-Y limb (Fig. 2). Again patency of the common hepatic duct was confirmed. It was clear that resection of the blind end of the Roux-en-Y limb was not beneficial, as cholangitis recurred;

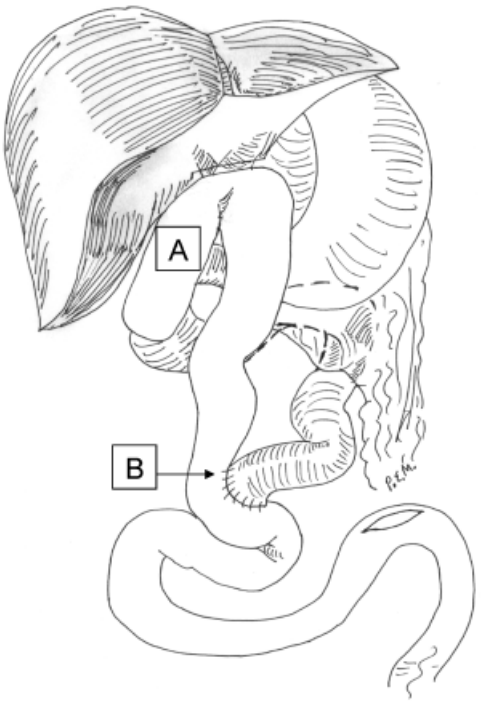

Fig. 1. The original Roux-en-Y hepaticojejunostomy was created to manage a bile leak after orthotopic liver transplantation (OLT) with choledochocholedochostomy. The jejunojejunostomy was fashioned as depicted (point B). At the initial revision, the blind end of the Roux-en-Y loop (A) was resected.

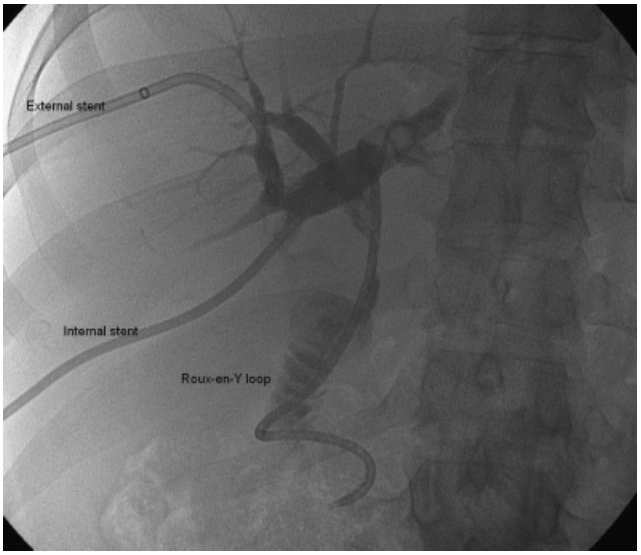

Fig. 2. A percutaneous transhepatic cholangiogram was performed via a superior right hepatic duct before Roux-en-Y limb lengthening. The initial images showed marked dilatation and absent flow into the jejunal limb, consistent with complete obstruction at the level of neo-hilum. An external drain was placed. This cholangiogram was obtained 1 week later after placement of a 10-French internal–external stent via an inferior right hepatic duct branch. Note decompression of the superior hepatic duct branches. The catheter tip is within the Roux-en-Y limb and contrast flows freely into the gut.

it furthermore was associated with obstruction of the common hepatic duct. Bile reflux persisted. The Roux-en-Y limb was lengthened from 30 to 90 cm by refashioning the jejunojejunostomy downstream (Fig. 3).

Two years after the second procedure, the patient enjoys good health and has been free of fever and abdominal pain and has not received any antibiotic therapy. His liver function remains normal.

Discussion

Biliary complications (leak, obstruction) account for half of the technical failures after OLT and typically require reoperation (1). Cholangitis may result from bile leak, obstruction, or occur in the presence of normal biliary drainage (2). Early cases may be related to instrumentation and the presence of foreign bodies, bacterial translocation from the gastrointestinal tract, impaired hepatic lymph drainage, and the high-level immunosuppression required in the early period after transplantation. Late infections in the setting of normal biliary drainage are rare. Orlando et al. (3) reported a single case of recurrent cholangitis after OLT with an intact hepaticojejunostomy. They proposed that a

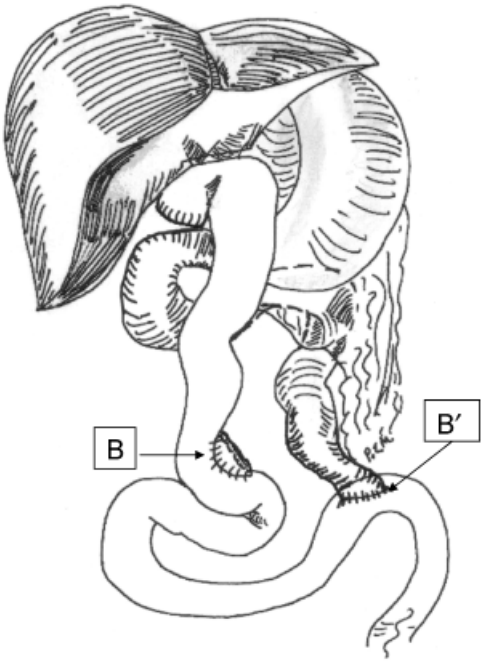

Fig. 3. The patient subsequently developed cholangitis and obstruction of the hepatic ducts requiring transhepatic stenting. The Roux-en-Y loop was lengthened by reanastomosing the proximal jejunum to the small bowel 60 cm distal to the initial anastomosis (takedown B with reanastomosis at B′). The blind loop is surgically absent from the first operation.

motility disorder might arise in the mobilized Roux-en-Y loop allowing the intestinal contents to reflux. An antireflux procedure was performed that prevented further infections. Similar consequences of dysmotility were observed following gastrointestinal reconstruction (4).

Millonig et al. (5) reported culture results from 172 bile samples obtained during ERCP from liver transplant recipients. Of these, 126 (73.3%) were positive for microbes. A total of 236 organisms were isolated: 114 (48.3%) gram-positive bacteria, 92 (39.0%) aerobic gram-negative, 8 (3.4%) anaerobes, and 22 (9.3%) fungi. The most common organism cultured from blood and bile is *E. coli* followed by other enteric gram-negative bacteria, including *Klebsiella*, *Pseudomonas*, and *Proteus* species. Polymicrobial infections with *Enterococci*, *Streptococcus viridans*, and other gram-positive bacteria are frequently encountered. These authors hypothesized that enteric organisms reach the biliary tree via the portal system. Under normal circumstances, these are efficiently cleared by host defense mechanisms. However, chronic immunosuppression and abnormalities of the biliary tree resulting in stasis, reflux, or obstruction predispose to symptomatic infection. Patients commonly present with right upper quadrant abdominal tenderness and fever, often accompanied by rigors, and jaundice. Common laboratory findings in cholangitis include increased WBC count, left shift with increased polymorphonuclear leukocytes, increased hepatic acute-phase reactants, elevated serum alkaline phosphatase level, and hyperbilirubinemia. Acute treatment consists of supportive care and antibiotics, as was frequently recommended for our patient. Definitive treatment for stone disease, strictures, and other anatomic abnormalities requires endoscopic or surgical intervention.

In the present case, prior studies and PTC confirmed a widely patent hepaticojejunostomy and the absence of bile duct strictures. The patient had been evaluated at 2 prior institutions. Surgical intervention was not judged to be beneficial; rather symptomatic treatment followed by suppressive therapy with antibiotics was recommended. This course of treatment failed to prevent episodes of fever and even sepsis. It is conceivable that many of these episodes of presumed cholangitis, especially those treated presumptively in the absence of blood cultures, were incorrectly diagnosed. Nonetheless, the patient had 2 prior episodes of bacteremia with a quinolones-sensitive *E. coli* treated with a prolonged course (3–6 weeks) of ciprofloxacin followed by cycled prophylactic antibiotics. Clinically, the patient responded to each treatment course. On presentation with septic shock to our center, the *E. coli* species was quinolones resistant, but not an extended β-lactamase producer. The sepsis resolved with imipenem/cilastin, but this failed to provide an indefinite cure.

We proposed 2 mechanisms to explain the recurrent cholangitis. Initially, we hypothesized that stasis in the blind loop promoted bacterial overgrowth resulting in episodic infection. However, amputation of the blind loop did not prevent further episodes of cholangitis and, in fact, the patient's condition worsened. We then concluded that the previous episodes of cholangitis and the present biliary obstruction were more likely the result of retrograde transit (reflux) of bile along the short Roux-en-Y limb. Initially, this resulted in a series of biliary tract infections that were responsive to antibiotics. After resection of the blind Roux-en-Y limb, inspissated bile and other material became lodged in the hepatic ducts. Importantly, the original hepaticojejunostomy was not narrowed, confirming the fact that biliary outflow obstruction was due to the accumulated debris in the intrahepatic ducts.

In this patient the 30-cm Roux-en-Y limb was physiologically inadequate. Collard and Romagnoli (4) demonstrated the presence of refluxed bile in 17/41 (41%) patients with a variety of Roux-en-Y jejunal loop reconstructions. Lengthening the Roux-en-Y loop from 60 to 110 cm cured 2 patients with severe symptomatic bile reflux. It is likely that the same principles apply after OLT as supported by at least 1 other case report demonstrating biliary reflux in this setting (3). Although this appears to be a rare complication of Roux-en-Y reconstructions, it is important to recognize the availability of surgical therapeutic options.

In the present case, medical therapies resulted in recurrent infections and antibiotic resistance in a patient with cholangitis following liver transplantation. Lengthening the efferent Roux-en-Y limb should be considered in the treatment of recurrent cholangitis occurring after hepaticojejunostomy.

References

1. Sherman S, Jamidar P, Shaked A, Goldstein LI, Busuttil RW. Biliary tract complications after orthotopic liver transplantation. Transplantation 1995; 60: 467–470.
2. Chuang JH, Lee SY, Chen WJ, et al. Changes in bacterial concentration in liver correlate with that in the hepaticojejunostomy after bile duct reconstruction: implication in the pathogenesis of postoperative cholangitis. World J Surg 2001; 25: 1512–1518.
3. Orlando G, Blairvacq JS, Otte JB, et al. Successful treatment of recurrent cholangitis after adult liver transplantation with a Tsuchida antireflux valve. Transplantation 2004; 77: 1307–1308.
4. Collard JM, Romagnoli R. Roux-en-Y jejunal loop and bile reflux. Am J Surg 2000; 179: 298–303.
5. Millonig G, Buratti T, Graziadei IW, et al. Bactibilia after liver transplantation: frequency and antibiotic susceptibility. Liver Transpl 2006; 12: 747–753.