Transpl Int (1996) 9: 161–163

BRIEF REPORT

Kris V. Kowdley
Karim A. Fawaz
Marshall M. Kaplan

Extrahepatic biliary stricture associated with cytomegalovirus in a liver transplant recipient

Received: 15 March 1995
Received after revision: 15 September 1995
Accepted: 29 September 1995

K.V. Kowdley (✉)[1] · K. A. Fawaz
M.M. Kaplan
Division of Gastroenterology,
Department of Medicine,
New England Medical Center,
Boston, MA, USA

[1] *Present address:* Division of
Gastroenterology,
University of Washington
School of Medicine, Box 356424,
1959 NE Pacific Street,
Seattle, WA 98195, USA
Fax: + 1 206 685 8684

Abstract We describe a patient who developed a stricture in the distal common bile duct 6 weeks after orthotopic liver transplantation. Histopathologic examination of the bile duct epithelium in the region of the stricture showed characteristic cytomegalovirus (CMV) inclusions. CMV was also identified in pulmonary alveoli and in the duodenum. Although CMV has been demonstrated in the biliary epithelium of AIDS patients with extrahepatic biliary strictures and biliary obstruction, this entity has not, to our knowledge, been described in liver transplant recipients. This report confirms that CMV infection should be included as a probable cause of extrahepatic biliary strictures and bile duct obstruction in liver transplant patients.

Key words Biliary stricture, CMV, liver transplantation · Liver transplantation, biliary stricture, CMV · CMV, biliary stricture, liver transplantation

Introduction

Strictures of the common bile duct associated with recent liver transplantation are usually a complication of the surgical procedure and have been ascribed to anastamotic breakdown, ischemia, or rejection [2]. Although cytomegalovirus (CMV) infection of the hepatobiliary tree has been reported to cause common bile duct strictures in patients with AIDS [5], this clinical entity has not been described in liver transplant recipients. We describe herein a patient who developed a common bile duct stricture associated with the presence of CMV in the bile duct epithelium following liver transplantation in the absence of other known causes for a post-liver transplant bile duct stricture.

Case report

A 45-year-old woman with end-stage liver disease due to primary biliary cirrhosis underwent orthotopic liver transplantation. The patient was CMV-negative; the donor's CMV status was unknown. No routine CMV prophylaxis therapy was used. The bile ducts were connected via a choledochocholedochostomy, and an intraoperative cholangiogram showed a patent anastamosis with good drainage of contrast into the duodenum. The patient initially did well, with a decrease in total serum bilirubin from 10.9 mg/dl to 4.8 mg/dl (normal 0.2–1.2 mg/dl); however, on the 3rd postoperative day, fever and worsening liver tests were noted. A repeat T-tube cholangiogram on the 9th postoperative day showed no evidence of obstruction or extravasation of contrast and a normal caliber bile duct. A liver biopsy was done and showed a mixed acute and chronic inflammatory infiltrate in the portal areas, as well as focal lymphocytic infiltration of the bile duct epithelium.These findings were felt to be most consistent with rejection, and the patient was treated with boluses of parenteral prednisolone for 2 days, with an improvement in liver tests. Over the next 10 days, liver tests improved and the total serum bilirubin on postoperative day 20 was 1.6 mg/dl, with an alkaline phosphatase of 293 U/l (nor-

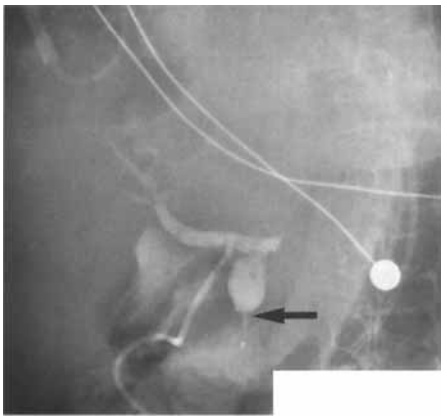

Fig. 1 T-tube cholangiogram showing a stricture in the distal common bile duct (*arrow*) with proximal dilatation

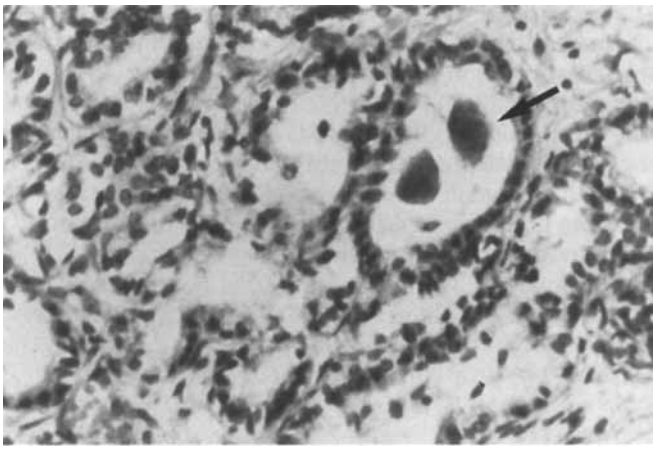

Fig. 2 Section of common bile duct with cytomegalovirus inclusions in bile duct epithelium (*arrow*)

mal up to 110 U/l), and normal aminotransferases; the T-tube was clamped. Over the next month, the patient's course was complicated by gram-negative pneumonia and one episode of melena. Upper endoscopy done on postoperative day 42 showed only prepyloric erythema.

Six weeks postoperatively, a culture of T-tube drainage, done because of fever, grew *Escheria coli* and *Klebsiella pneumoniae*, despite adequate antibiotic coverage. A T-tube cholangiogram performed on postoperative day 50 showed a localized stricture in the distal common bile duct, with proximal dilatation (Fig. 1). An endoscopic retrograde cholangiopancreatogram (ERCP) showed a normal pancreatic duct and again showed the stricture in the distal common bile duct. A repeat T-tube cholangiogram performed 4 days later demonstrated the stricture, as noted above, and showed evidence of a choledochoduodenal fistula. The patient was taken to the operating room, where a 2-cm perforation of the second portion of the duodenum and a stricture in the distal common bile duct were found. The choledochoduodenal fistula could not be located, but an intraoperative T-tube cholangiogram showed dilatation of the distal common bile duct to 2 cm and passage of contrast material into the duodenum. An intraoperative needle biopsy of the liver showed acute hepatocellular necrosis, fatty change, and possible evidence of CMV inclusions; no specific antiviral therapy was administered. The patient continued to do poorly postoperatively, with worsening pulmonary infiltrates and hypoxemia. She died 11 weeks after transplantation.

At autopsy, the liver was moderately congested and had marked, widespread, fatty change. No evidence of CMV infection within the liver parenchyma was noted. All vascular and biliary anastamoses were intact. In the right lobe of the liver, there were two nodules deep within the organ composed of large, pleomorphic, neoplastic-appearing lymphocytes, consistent with a large cell lymphoma. Markers for kappa and lambda light chains showed a polyclonal pattern of staining.

The common bile duct was narrowed in the region of the ampulla with proximal dilatation; the proximal bile duct was filled with bile and sludge. No fibrosis of the wall of the common bile duct was noted, but cytomegalic inclusions were present in the mucosa and submucosal glands in the narrowed region, as well as throughout the course of the duct (Fig. 2). The duodenal mucosa adjacent to the perforation site also contained cytomegalic inclusions.

Discussion

This patient developed an extrahepatic biliary stricture 6 weeks after orthotopic liver transplantation, associated with CMV infiltration of the stricture, in the absence of other causes for post-transplant bile duct stricture. Bile duct complications in the immediate postoperative period following liver transplantation are usually related to the surgical procedure [1, 2]. Despite significant advances in surgical technique, bile leaks and biliary tract obstruction are important causes of morbidity and often necessitate reoperation [2]. Biliary complications are common and have been reported in up to one-third of all liver transplantations [8]. Bile leaks can be seen 1–2 weeks after liver transplantation and are typically associated with the appearance of bile in the abdominal drains [2]. Bile peritonitis may occur if there is spillage of bile into the peritoneal cavity, causing a chemical peritonitis [2, 4]. Bile duct obstruction may be due to strictures, bacterial cholangitis, or other causes.

Strictures of the biliary tree in liver transplant patients may be classified into anastomotic and nonanastomotic varieties. While anastomotic strictures have usually been reported to be a direct consequence of the surgical procedure itself, nonanastomotic strictures have been less well understood. The suggested causes include ischemia, rejection, or infection. Extrahepatic biliary strictures have been described in association with CMV infection in patients with AIDS, as part of the so-called syndrome of AIDS cholangiopathy [3, 5]; the diagnosis has been established in some cases by the demonstration of CMV inclusions in the bile duct epithelium [3, 5]. In contrast to AIDS patients, histopathologic findings of CMV have not been demonstrated in the bile duct epithelium of liver transplant patients with biliary strictures, not even in those with systemic CMV infection or CMV hepatitis [5].

There is some indirect evidence that CMV may be involved in the pathogenesis of biliary strictures in the liver transplant patient. Studies on the so-called vanishing bile duct syndrome suggest there is an interrelationship between bile duct injury and CMV infection in liver transplant patients [6, 7]. The virus is felt to have a proclivity to invade bile duct epithelium, at least in neonates [7]. It has been reported that CMV infection and the degree of donor/recipient HLA antigen matching may together increase the risk of vanishing bile duct syndrome [6].

The identification of CMV in similar extrahepatic strictures from patients with AIDS cholangiopathy, as well as the intriguing association between CMV and vanishing bile duct syndrome suggest that this virus may be an etiologic agent in the pathogenesis of extrahepatic biliary strictures in patients who have undergone liver transplantation. Our observation suggests that cytopathologic changes in the biliary tree caused by CMV are not unique to AIDS patients but rather can occur in other immunosuppressed patients with ongoing CMV disease, particularly in liver transplant recipients.

References

1. Busuttil RW, Colonna JO II, Hiatt JR, Brems JJ, Khoury GE, Goldstein LI, Quinones-Baldrich WJ, Abdul-Rasool IH, Ramming KP (1987) The first 100 liver transplants at UCLA. Ann Surg 206: 387–402
2. Carithers RL, Fairman RP, Mendez-Picon G, Posner MP, Mills AS, Friedenberg KT (1988) Postoperative care. In: Maddrey WC (ed) Transplantation of the liver. Elsevier, New York, p 111
3. Cello JP (1989) Acquired immunodeficiency syndrome cholangiopathy: spectrum of disease. Am J Med 86: 539–546
4. Krom RAF, Weisner RH, Rettke SR, Ludwig J, Southorn PA, Hermans PE, Taswell HF (1989) The first 100 liver transplantations at the Mayo Clinic. Mayo Clin Proc 64: 84–94
5. Margulis SJ, Honig CL, Soave R, Govoni AF, Mouradian JA, Jacobson IM (1986) Biliary tract obstruction in the acquired immunodeficiency syndrome. Ann Intern Med 105: 207–209
6. O'Grady JG, Alexander GJM, Sutherland S, Donaldson PT, Harvey F, Portmann B, Calne R, Williams R (1988) Cytomegalovirus infection and donor/recipient HLA antigens: interdependent cofactors in pathogenesis of vanishing bile duct syndrome after liver transplantation. Lancet (II) (2): 302–305
7. Sherlock S (1987) The syndrome of disappearing intrahepatic bile ducts. Lancet (II) (2): 493–496
8. Ward EM, Kiely MJ, Maus TP, Weisner RH, Krom RAF (1990) Hilar biliary strictures after liver transplantation: cholangiography and percutaneous treatment. Radiology 177: 259–263