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Clinicopathologic findings of recurrent primary sclerosing cholangitis after orthotopic liver transplantation

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Abstract: Whether primary sclerosing cholangitis (PSC) occurs after orthotopic liver transplantation is controversial, largely because the pre-transplant diagnosis of PSC is based on nonspecific radiological and histological findings. We reviewed clinical, radiological, and histological records of 53 patients who underwent liver transplantation for PSC between 1985 and 1998. Three patients with patent hepatic arteries and no evidence of chronic rejection had radiological and histological findings that may have been due to recurrent PSC. Bile duct stricturing in these patients proved permanent and progressive and affected both the quality of life and graft survival. The first patient, who is 110 months after transplantation, has had repeated episodes of cholangitis for the last year. The second patient underwent excision of a strictured hepatic duct 45 months after transplantation and was ultimately retransplanted 95 months after initial transplantation. The third patient underwent left hemihepatectomy of an atrophied lobe 50 months after transplantation. Although the patient population assessed in this study is limited, putative recurrent PSC in the allografts has led either to graft loss or to clinically significant hepatobiliary complications of the graft.

Key words: orthotopic liver transplantation, primary sclerosing cholangitis, recurrence, biliary stricture

Introduction

Although the pathogenesis of primary sclerosing cholangitis (PSC) remains uncertain, this chronic disease is felt to be autoimmune in origin. PSC is clinically characterized by intractable elevation of cholestatic serum liver enzymes, and several cholangiographic features such as multifocal strictures and segmental dilatation. In addition, suggestive but non-specific histological features (lymphoplasmacytic inflammation with epithelial disruption, concentric fibrosis around bile ducts with edema leading to fibroobliteration of bile ducts, and bile ductular proliferation with portal fibrosis) are well documented. The natural history of PSC is variable but is often serious and progressive, with patients having a median survival of 10 to 12 years after diagnosis.[1,2] For patients with end-stage PSC, orthotopic liver transplantation (OLT) is the best treatment currently available.[3–6] As the number of long-term survivors transplanted for PSC has grown, the possibility of disease recurrence has emerged. The diagnosis of PSC is based on cholangiographic features and a combination of clinical, laboratory, and histologic findings. However, none of these features is specific to PSC. In particular, biliary strictures in the allografts can occur due to a variety of insults including hepatic arterial thrombosis, ischemia associated with prolonged cold preservation, chronic rejection, and ABO-incompatible allografts. Primary or secondary biliary infection may also contribute to biliary strictures.[7] In view of this, whether recurrent PSC occurs after OLT is still controversial and the natural history of any such recurrence remains to be elucidated.

In this study, we report three patients in whom it was strongly suspected that recurrent PSC occurred after OLT; the clinical significance of these observations is discussed.

Patients and methods

All patients who underwent OLT by the Qreensland Liver Transplant Service between 1985 and 1998 were reviewed. For patients to be diagnosed with recurrent PSC, the following criteria were required: (1) clinical, cholangiographic, and histological features consistent

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with PSC in the native liver, (2) post-OLT symptoms of jaundice or cholangitis, (3) nonanastomotic strictures of intrahapatic and/or extrahepatic bile ducts, demonstrated on cholangiography post-OLT, (4) histological features consistent with PSC in allograft livers, such as epithelial ulceration, periductal fibrosis, inflammation around larger bile ducts, and changes in small bile ducts, including duct scars, ductular proliferation, and periductal fibrosis, (5) Doppler ultrasound or angiographic evidence of normal arterial supply of the transplanted liver.

Results

There were 53 patients (27 male and 26 female; mean age, 43 years; range, 15–64 years) with PSC who underwent orthotopic liver transplantation between 1985 and 1998. Forty-seven patients had a whole liver graft and 6 patients had a right lobe graft. Five-year patient survival was 69.8%.

Three of the 53 patients fulfilled our criteria for recurrent PSC and their details are presented below. In these three patients, there was no significant prolongation of graft cold ischemic time, and no intraoperative or postoperative vascular complications were evident. The blood types between donors and recipients were compatible.

Case 1

A 15-year-old female underwent liver transplantation in November 1989. Ten months after surgery she developed persistently abnormal liver function test results, with a gamma-glutamyl transferase (G-GT) rising to a peak of 529 IU/l. A percutaneous transhepatic cholangiogram (PTC) 11 months after transplantation was normal. A laparotomy was performed and no biliary obstruction was seen. A liver biopsy taken at surgery showed non-specific portal inflammation which was not diagnostic of rejection. Her G-GT remained persistently abnormal. A liver biopsy performed 16 months after transplantation demonstrated heavy periductal inflammation and ulceration of a large bile duct in the liver core (Fig. 1). Similar changes were seen in a further biopsy 28 months post-transplant and there were additional findings of periductal fibrosis ("onion skinning") and fibrous linkage between portal tracts. A PTC performed 48 months after transplantation showed diffuse stricturing of the biliary tree. Despite these changes, the patient remained asymptomatic. However, 82 months after transplantation, she suffered an episode of cholangitis. A PTC demonstrated marked irregularity and stricturing of intrahepatic ducts with mild dilatation of the left duct (Fig. 2). Since January 1998 (98 months after transplantation), she has been admitted five times because of repeated cholangitis. A further biopsy showed portal-to-portal fibrous linkage, periductal edema and fibrosis, and focal bile duct loss. Retransplantation is being considered.

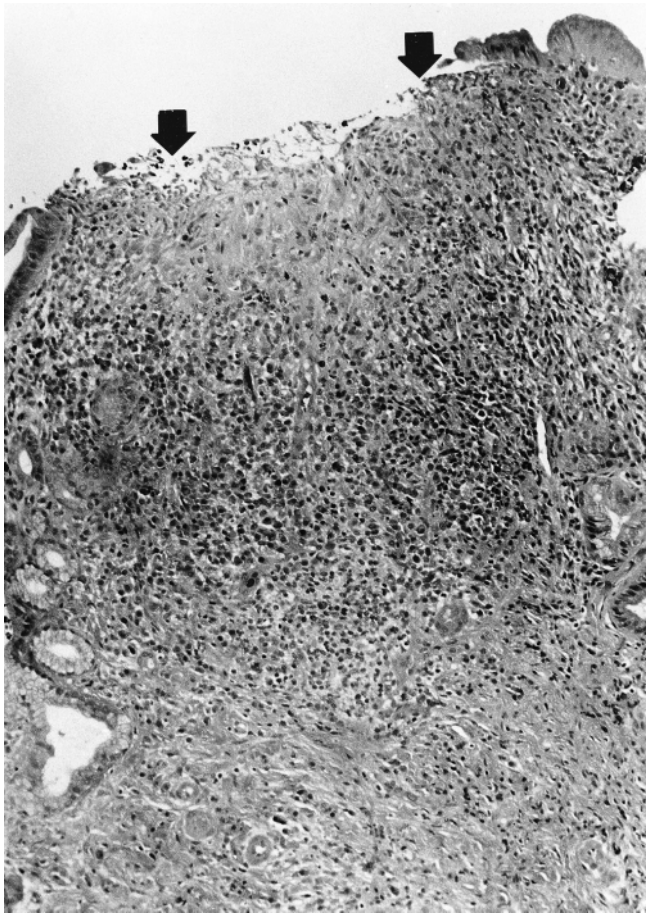

Fig. 1. A large duct sampled in the biopsy shows ulceration of the epithelial surface (*arrowed*) surrounded by a heavy lymphoplasmacytic inflammatory infiltrate (case 1). H&E, ×250

Case 2

A 22-year-old man underwent liver transplantation in May 1990. His post-operative course was uneventful and his liver function test results returned to normal. He developed persistently abnormal liver function test results with a rising G-GT 12 months after liver transplantation. A liver biopsy at that stage showed acute cellular rejection and he was treated with intravenous methylprednisolone. He also underwent a PTC shortly after the biopsy and this was normal. His liver function test results, however, remained abnormal. Twenty-four months post-OLT a further liver biopsy

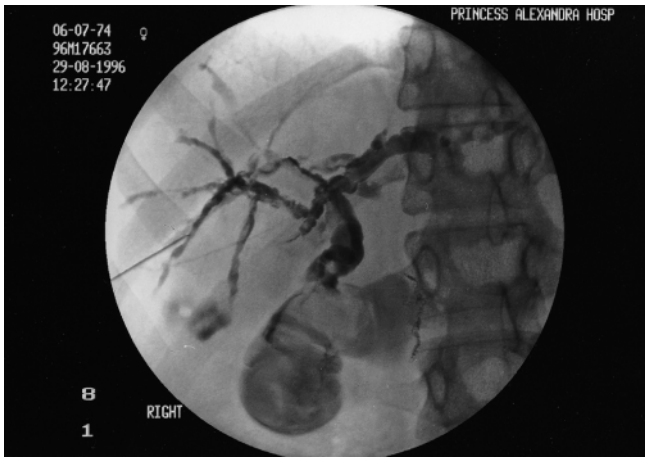

Fig. 2. Percutaneous transhepatic cholangiogram demonstrating irregularity and stricturing of the intrahepatic biliary tree with dilatation of the left hepatic duct 82 months post-orthotopic liver transplantation (OLT) (case 1)

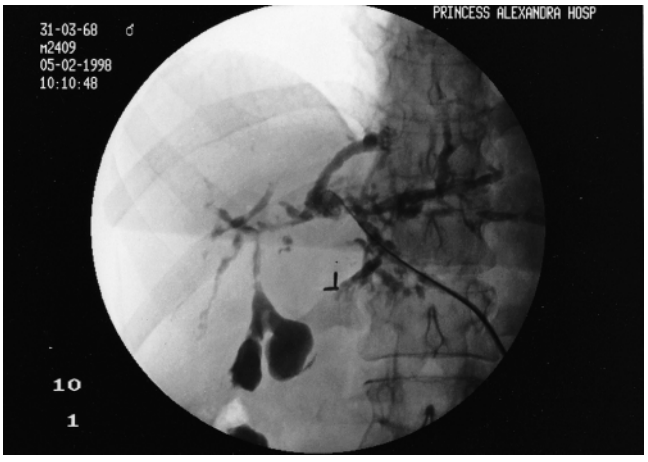

Fig. 3. Percutaneous transhepatic cholangiogram showing marked irregularity and stricturing of the entire intrahepatic biliary tree with associated focal biliary dilatation 92 months post-OLT (case 2)

was performed. This showed ulceration and heavy inflammation of a large bile duct within the liver core. He subsequently developed anorexia, lethargy, and loss of weight with a further deterioration in liver function test results 40 months after transplantation. A PTC performed at this time demonstrated diffuse stricturing of the biliary tree with a prominent stricture in the common hepatic duct. The strictured hepatic duct was excised and the choledochojejunostomy revised 45 months after transplantation. A liver biopsy taken at operation demonstrated periductal fibrosis, inflammation, and deposition of copper-associated protein due to chronic cholestasis. The excised hepatic duct segment demonstrated ulceration with proliferation of granulation tissue and a heavy lymphoplasmocytic infiltrate in the periductal stroma. The periductal arteries and veins were unremarkable. These features were similar to those seen in the earlier biopsy. His liver function test results remained persistently abnormal despite the surgery. Ninety-two months after transplantation, the serum level of total bilirubin was elevated, at 61 μmol/l. An ultrasound showed intrahepatic duct dilatation, and a subsequent PTC showed marked irregularity of the entire intrahepatic biliary tree with multiple strictures and adjacent areas of focal dilatation (Fig. 3). In April 1998, he underwent retransplantation, 95 months after OLT. The failed graft showed multifocal large duct scarring associated with chronic inflammation, ulceration, and luminal narrowing. The histological features were typical of PSC (Fig. 4).

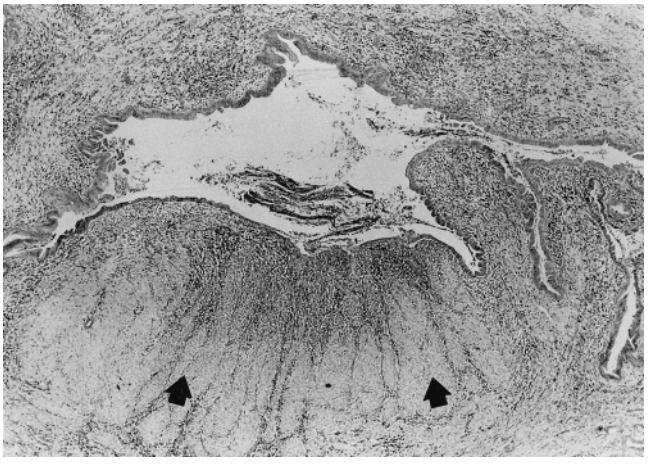

Fig. 4. Large duct changes typical of primary sclerosing cholangitis in an excised allograft. The duct is ulcerated and lamellar fibrous scarring affects part of the wall (*arrowed*) (case 2). H&E, ×40

Case 3

A 39-year-old man who underwent OLT in December 1988 developed persistently abnormal liver function test results 7 months after transplantation, with a peak G-GT level of 300 IU/l 9 months after transplant. His liver function test results fluctuated quite widely but remained abnormal. A stent cholangiogram performed 1 month after transplantation was normal. Forty-five months after transplantation, he developed recurrent right upper quadrant pain and underwent a PTC which demonstrated a tight stricture of the left hepatic duct and more minor strictures of the right hepatic duct (Fig. 5). He subsequently underwent left hemihepatectomy 50 months after transplantation, and histology demonstrated heavy lymphoplasmacytic inflammatory infiltrate around the large hilar bile ducts with associated ulceration and periductal fibrosis. Within

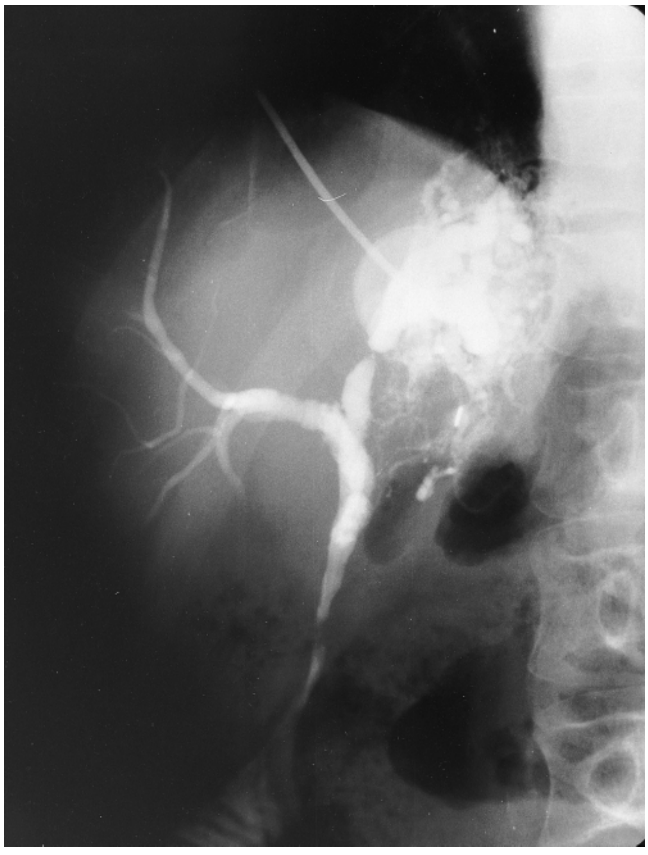

Fig. 5. Percutaneous transhepatic cholangiogram demonstrating a tight left hepatic duct stricture and minor stricturing of the right hepatic duct 45 months post-OLT (case 3)

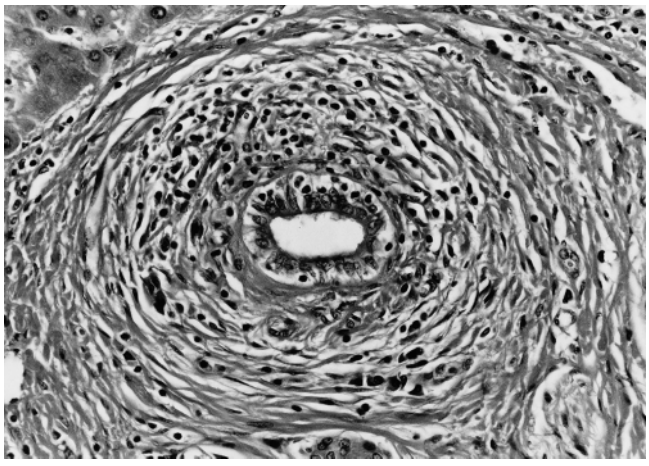

Fig. 6. Periductal onion-skinning fibrosis around a small bile duct in a hemihepatectomized allograft (case 3). H&E, ×250

the liver there was portal fibrosis with linkage and periductal fibrosis (Fig. 6). These features were suggestive of recurrent PSC. He has remained asymptomatic since surgery. At 78 months after OLT, an ultrasound showed normal liver texture with no bile duct dilatation and normal vascular flow.

Discussion

We describe three patients transplanted for PSC who have developed biochemical, histological, and cholangiographic features of recurrent disease that became apparent 16 months to 4 years after transplantation.

Although it is controversial as to whether recurrent PSC develops after OLT, there have been several recent reports which suggest that PSC does recur. Sheng et al.[8] reported that intrahepatic and nonanastomotic extrahepatic biliary strictures were significantly more common in patients who had undergone liver transplantation for PSC than in patients who received allografts for other end-stage liver diseases and in whom choledochojejunostomies were fashioned. The investigators concluded that the nonanastomotic biliary strictures were possibly caused by recurrent PSC, because no other process could be invoked to explain the higher prevalence of these strictures. Other investigators have confirmed these findings.[9,10] Sheng et al.[11] subsequently described the post-OLT cholangiographic features of patients transplanted for PSC. Nonanastomotic strictures were different from those of other OLT patients, with a higher prevalence of mural irregularity and diverticulum-like outpouchings in the PSC group.

There is also histological evidence to suggest that PSC recurs after OLT. Harrison et al.[12] compared patients who underwent transplantation for PSC with a similar number of patients who underwent transplantation for conditions other than PSC and in whom choledochojejunostomies were performed. Seventeen of 22 patients who underwent OLT for PSC had post-OLT biopsy findings suggestive of PSC (features of biliary obstruction, fibrous cholangitis, and fibro-obliterative lesions) as compared with 4 of the 22 non-PSC patients. Histological changes such as large duct inflammation and periductal fibrosis can occur in several conditions including PSC, localized ischemia, and anastomotic stricturing. Bile duct scars (fibroobliterative lesions) may be more suggestive of PSC,[12] but were not features in our patients, possibly reflecting a relatively early time point in the disease course. More importantly, it is the constellation of clinical and pathological changes rather than a single feature that is important in diagnosing PSC. Our three patients are notable in that typical clinical, biochemical, cholangiographic, and histological features occurred concurrently and in that their clinical progress resembled that normally seen in patients with PSC.

The effects on graft function and patient survival in patients with putative recurrent PSC have received scant attention. In the short-to-medium term, it has been reported that recurrent PSC does not affect the quality of life or patient or graft survival.[5,13] Contrary to these reports, in our three patients, graft loss or significant hepatobiliary complications occurred after 9, 8, and 4 years, respectively. Since PSC is a protracted and progressive disease, long-term follow-up may be required to assess the affect on allograft and patient survival in patients developing recurrent disease. This is confirmed by a recent report that showed that patient and graft 5-year survival in recurrent PSC was significantly lower compared with survivals in those patients in whom features of recurrent PSC did not develop.[14]

Although the patient population assessed in this study was limited, features of recurrent PSC in the allografts did occur and led to graft loss or relatively severe graft compromise which required surgical intervention. If PSC does recur, then our data suggest that it is likely to be of clinical significance.

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