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CASE REPORT

# Cholangiocarcinoma complicating recurrent primary sclerosing cholangitis after liver transplantation

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## Summary

*De novo* cholangiocarcinoma associated with recurrent primary sclerosing cholangitis in the transplanted liver is rare. This case report reviews the literature and highlights the need to consider cholangiocarcinoma in transplanted patients with PSC that clinically/biochemically deteriorate.

## Introduction

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by progressive inflammation and fibrosis of intrahepatic and extrahepatic bile ducts leading to multifocal strictures. The aetiology of PSC is considered to be a combination of immunological mechanisms, genetic susceptibility and a disorder of biliary epithelia. The diagnosis is based on cholestatic biochemistry and cholangiography demonstrating multifocal biliary strictures with secondary causes of sclerosing cholangitis excluded [1]. The endpoint of PSC is biliary cirrhosis, portal hypertension and hepatic decompensation [1,2].

The mean time from PSC diagnosis to death or transplantation ranges from 9.6 to 12 years, with cholangiocarcinoma developing in 8–13.2% of patients [3,4]. Indications for transplantation include complications of portal hypertension, impaired quality of life and chronic liver failure. But indications peculiar to PSC are pruritus, recurrent cholangitis and selected cases of hilar cholangiocarcinoma [5–7].

Five-year survival rates for transplantation of greater than 80% are being reported. Post-transplant recurrence of PSC occurs in 20–25% based on histological and radiological criteria, but it can be difficult to distinguish from chronic rejection, preservation injury or donor after cardiac death cholangiopathy [1,8]. The subsequent development of cholangiocarcinoma with PSC in the transplanted liver is rare with a single previous case report [9].

## Case report

A 22 year male was transplanted with a heart beating whole graft in 1993. Implantation technique was piggyback and hepaticojejunostomy for biliary reconstruction. He had been diagnosed with PSC and ulcerative colitis (UC) 1 year before. The explanted liver had no evidence of cholangiocarcinoma or dysplasia. Four years after transplant he developed cholestasis and percutaneous

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transhepatic cholangiography (PTC) demonstrated an intrahepatic cholangiopathy with no anastomostic component. Hepatobiliary iminodiacetic acid scan excluded Roux loop dysfunction and biopsy showed periductal fibrosis and pericholangitis. PSC recurrence was diagnosed and treated with ursodeoxycholic acid (UDCA) 250 mg twice daily with improvement in liver function and weight. Maintenance immunosuppression was Cyclosporin A 150 mg twice daily and Azathioprine 75 mg once daily.

Surveillance colonoscopy during this time was normal. Eight years post-transplant he became cholestatic with serum total bilirubin 17 [normal range (NR) 3–20 μmol/l], aspartate aminotransferase (AST) 69 [NR 10–50] IU/l, alkaline phosphatase (ALP) 410 [NR 30–130] IU/l and gamma-glutamyl transferase (GGT) 329 [NR 1–55] IU/l. Ultrasound was normal. Liver biopsy showed no significant progression in fibrosis and pericholangitic activity was mild consistent with PSC. His UDCA was increased to 500 mg twice daily and immunosuppression remained unchanged. At subsequent clinical reviews he remained physically active, with stable UC and mildly cholestatic liver function tests.

Sixteen years post-transplant he started to experience fatigue and was admitted with a *Streptococcus viridans* cholangitis. Liver function tests included serum total bilirubin 98 [NR 3–20] μmol/l, AST 71 [NR 10–50] IU/l, ALP 686 [NR 30–130] IU/l and GGT 479 [NR 1–55] IU/l. CT, MRCP and PTC demonstrated a cholangiopathy with marked dilation of the intrahepatic ducts, but no dominant stricture. CA19-9 was 98 (NR < 37) kU/l. He improved with intravenous antibiotics and was discharged on oral antibiotics. A week later he presented septic shock requiring a 3 day admission to the intensive care unit for pressor support. Repeated CT showed the development of more liver abscesses and CT angiography excluded an ischemic component.

His MELD was 19, Child Pugh score 9 (B) and a decision was made to relist. He was retransplanted with a whole heart beating liver. Operative findings were of an enlarged liver (3730 g), moderate portal hypertension with pus within the graft. Macroscopically there was no evidence of malignancy. An enlarged hilar lymph node was sent for frozen, which excluded post-transplant lymphoproliferative disease and malignancy.

Histological assessment of the explant revealed extensive cystic dilatation of the intrahepatic ducts (Fig. 1a). A hard and ill-circumscribed mass measuring 35 × 27 × 17 mm was found in the hepatic hilum (Fig. 1b). There were also multiple nodules (4–9 mm) on a background of noncirrhotic, cholestatic parenchyma. On microscopy, the hilar mass was a moderately to poorly differentiated adenocarcinoma (Fig. 2) with a small focus of spindle cell


**Figure 1** Macroscopic images of the explanted liver. (a) Extensive cystic dilation of the intrahepatic large bile ducts and parenchymal nodules. (b) Cross-sections of the hilar mass reveal an ill-circumscribed solid tumour round a hilar bile duct.

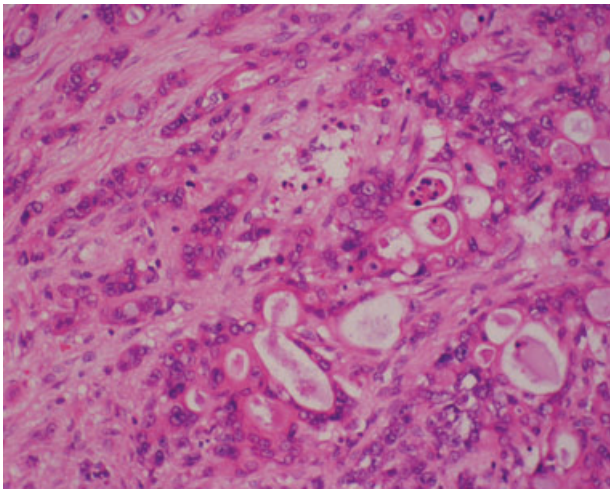

**Figure 2** Microscopic image of the explanted liver. The tumour consists of poorly differentiated tubular adenocarcinoma (H&E × 200).

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transformation (pseudosarcomatous change). Dysplastic epithelium was noted in the adjacent bile duct. The tumour diffusely infiltrated into bile duct wall and periductal connective tissue, with focal involvement of hilar adipose tissue and liver parenchyma. Foci of vascular, lymphatic, and perineural invasion were present. The parenchymal nodules showed similar histological features, consistent with intrahepatic metastases. On immunostaining, tumour cells were diffusely positive for cytokeratin (CK) 7, CK19, CA19-9 and mucin core protein 1 (MUC1), and negative for CK20. Resection margins and hilar lymph nodes were tumour free. The background parenchyma showed lobular distortion with periportal fibrosis and bridging. Peripheral portal tracts showed periductal concentric fibrosis with bile duct damage several foci of bile duct loss, and a large amount of copper-associated protein deposition on Orcein, consistent with recurrent PSC.

The tumour was histologically diagnosed as cholangiocarcinoma based on a bile duct centred adenocarcinoma and the presence of dysplastic epithelium in the adjacent bile duct. The diagnosis was also supported by the diffuse positivity for CK7, CK19, CA19-9 and MUC1, all of which are commonly expressed in biliary epithelium or cholangiocarcinoma. A cholangiocarcinoma arising from the native duct was excluded given that there was no evidence of cholangiocarcinoma or biliary dysplasia in the 1993 explant and a hepaticojejunostomy rather than a duct to duct reconstruction was used. Further molecular analyses, such as genotyping by microsatellite analysis [10], to distinguish donor from recipient origin of the cholangiocarcinoma was not performed.

He had an uneventful postoperative course and was discharged on day 15. Maintenance immunosuppression was sirolimus 3 mg once daily and prednisolone 15 mg once daily. Staging CT–PET revealed multiple bone metastases and he was started on adjuvant chemotherapy (fluorouracil and cisplastin). Six months later he started to experience chest pain and shortness of breath. CT pulmonary angiography demonstrated progressive metastatic disease. His chemotherapy regime was changed to gemcitabine and cisplastin, and his immunosuppression was reduced to sirolimus 1 mg once daily. The patient died 7 months after retransplantation.

## Discussion

Chronic inflammatory diseases such as PSC are associated with an increased risk of cancer [10]. Cholangiocarcinoma is found in 8–13.2% of PSC patients, with 5% being identified within a year of PSC diagnosis [4]. Occult cholangiocarcinoma is found in 3% of explanted PSC livers at transplant. It has been estimated that the annual incidence of cholangiocarcinoma in PSC is 1–1.5% and is a leading cause of death [11]. The risk factors for developing cholangiocarcinoma in PSC are not established, smoking and alcohol have been suggested but duration of PSC has not been found to be associated [12]. The survival figures for cholangiocarcinoma in PSC are poor with the majority not surviving beyond 2 years [13]. Surgical resection offers a prospect of cure with a 5-year survival of 25–40% [14] and in selected patients transplantation following neoadjuvant therapy a 70% 5-year actuarial survival is being reported [5–7].

Recurrent PSC develops in 20–25% of transplants 5–10 years later [8,15,16]. Risk factors for recurrent PSC are not understood but include intact colon, male sex, active colitis being treated with steroids, cholangiocarcinoma prior to transplant and acute cellular rejection. The long-term sequelae on survival is not clear with some groups saying that it has no impact [17] while others report reduced graft survival [15,18], with up to a third of patients requiring retransplantation at a median of 5 years [16].

Compared with the general population, *de novo* cancer is more common after transplant and is one of the main causes of late mortality [19]. The incidence of *de novo* cancer varies from 2% to 16%, depending on the length of follow up and era of transplantation [19]. In PSC, the probability of developing a non-skin cancer is highest with an incidence of 22% at 10 years [19]. Considering the recurrence rate of PSC *de novo* cholangiocarcinoma is surprisingly rare. In our institution, 178 transplants for PSC have been performed since 1989, eight of which have required retransplantation for recurrent PSC. Excluding the present case, none of the explants had any evidence of dysplasia or cancer. The only other case in the literature is of a 22-year-old male who was transplanted in 1990. This was complicated by bile leak requiring a hepaticojejunostomy, and retransplantation in 1992 for chronic biliary sepsis. Maintenance immunosuppression was Cyclosporin A and prednisolone. In 1999, he was diagnosed with recurrent PSC, no colitis and relisted. Whilst on the waiting list, he was diagnosed with hilar cholangiocarcinoma. He was treated with neoadjuvant chemoradiotherapy and successfully retransplanted in 2001 [9].

Transplanted patients with evidence of recurrent PSC associated with deterioration in their constitutional performance status or liver biochemical parameters should undergo evaluation with the possibility of an underlying cholangiocarcinoma being considered. With there being only two cases, it is difficult to draw any further conclusions but the rarity of *de novo* cholangiocarcinoma maybe related to immunosuppression altering the microenvironment produced by chronic inflammation that facilitates the dysplastic carcinoma transformation [20].

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## Authorship

SEK and YZ: wrote the paper. SS: collected data. NH and WJ: conceived, critically reviewed and approved the paper. KA: critically reviewed and approved the paper.

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