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Predicting cholangiocarcinoma in patients with primary sclerosing cholangitis before transplantation

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Abstract

Patients with primary sclerosing cholangitis are at an increased risk of developing cholangiocarcinoma, which is difficult to diagnose because the biliary tree is already distorted. Eleven patients with primary sclerosing cholangitis who underwent orthotopic liver transplantation at this hospital were evaluated. Four patients had coincidental histologically proved cholangiocarcinoma. Patients with cholangiocarcinoma in contrast to patients without tumour presented with rapid onset of persistent jaundice, pruritus, and weight loss associated with an appreciable rise in bilirubin (8× *v* 2×) and alkaline phosphatase (3·5× *v* 1·2×) over one year. Cholangiography and computed tomography showed appreciably dilated intrahepatic bile ducts (3/4 *v* 0/7). The diagnosis of cholangiocarcinoma could only be established before operation in one patient by fine needle aspiration cytology. Tumour was recognised at operation in one other. Histological examination of hepatectomy specimens showed that patients with cholangiocarcinoma had less advanced histological features of primary sclerosing cholangitis. Multiple areas of carcinoembryonic antigen positive epithelial atypia and carcinoma in situ were found in all patients with cholangiocarcinoma. Cholangiocarcinoma recurred in two patients at 14 and 39 months after transplantation. Superimposed cholangiocarcinoma can be predicted in most patients with cholangitis before transplantation, although a definitive diagnosis is difficult to make. Their prognosis after successful transplantation is guarded.

Primary sclerosing cholangitis is a chronic cholestatic disorder of unknown cause characterised by multiple fibrotic strictures of the intra and extrahepatic bile ducts. The rate of progression of the disease is unpredictable, although up to 49% of symptomatic patients eventually develop biliary cirrhosis and liver failure.[1] Thus increasing numbers of patients with primary sclerosing cholangitis are being considered for liver transplantation. Currently, it is the second most common indication for adult liver transplantation at our institution.[2]

Recent reports suggest that patients with primary sclerosing cholangitis are at an increased risk for the development of cholangiocarcinoma,[3–5] This fatal complication is, however, difficult to diagnose due to the distorted biliary tree. Currently, the only methods of detecting cholangiocarcinoma with absolute certainty in these patients is complete examination of the liver and biliary tree at necropsy or more recently after total hepatectomy. The aim of this study was to determine clinical, laboratory, and radiological features of patients with end stage primary sclerosing cholangitis which predicted superimposed cholangiocarcinoma.

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Methods

All adult patients undergoing orthotopic liver transplantation at this hospital from January 1985 to September 1989 were evaluated for primary sclerosing cholangitis. A diagnosis was made if patients satisfied three criteria: (a) typical cholangiographic findings (multiple strictures, diverticula) of the intra or extrahepatic bile ducts shown by endoscopic retrograde cholangiography (ERCP) or percutaneous transhepatic cholangiography (PTC); (b) histological examination of the total hepatectomy specimen suggestive of the disease (periportal fibrosis, fibrous obliterative cholangitis, or biliary cirrhosis); (c) no other cause for biliary cirrhosis.

Patients who met these criteria were divided into two groups depending on the presence or absence of coincidental cholangiocarcinoma documented in the hepatectomy specimen. Clinical, laboratory, radiological, and histological features of both groups were compared. Clinical parameters assessed were indications for transplantation, age, duration (years) of colitis (histologically proved), duration (years) of primary sclerosing cholangitis (from the time of compatible cholangiographic or histological evidence), and previous operations. Laboratory test results recorded were serum bilirubin, albumin, prothrombin time, fibrinogen, alkaline phosphatase, aspartate transaminase, γ glutamyl-transferase, and carcinoembryonic antigen. The increase in bilirubin and alkaline phosphatase over 12 months before operation was calculated as a ratio (concentration at the time of transplantation divided by the concentration one year before).

Cholangiograms (PTC or ERCP) were assessed by one radiologist for the presence of a dominant stricture and progressive dilation (if sequential films were available). Pronounced ductal dilatation was diagnosed (according to criteria proposed by MacCarty *et al*[6]) if the diameter of the common bile duct was greater than 2·0 cm, left hepatic duct greater than 1·0 cm, right hepatic duct greater than 0·8 cm, or intrahepatic ducts greater than 0·5 cm. As the magnification factor could not be corrected, measurements were approximate. The presence of mass lesions on computed tomography or ultrasound was recorded. Attempts to exclude extrahepatic spread of suspected tumour before transplantation included technetium methylene diphosphonate bone scanning, computed tomo-

TABLE I *Clinical features of patients with primary sclerosing cholangitis and with coincidental cholangiocarcinoma*

	Primary sclerosing cholangitis		
	Alone	*With cholangiocarcinoma*	*p value*
No (males)	7 (3)	4 (1)	
Age (years) (range)	40 (17–48)	41 (32–45)	NS
Indication for transplant:			
End stage cirrhosis	7	–	
Sudden jaundice/pruritus	–	3	
Recurrent cholangitis	2	1	
Inflammatory bowel disease:			
Frequency	7	3	NS
Mean (range) duration (years)	19·7 (1–38)	15·3 (2–28)	NS
Primary sclerosing cholangitis			
Mean (range) duration (years)	8·6 (3–15)	7 (1–14)	NS
Previous operations:			
Cholecystectomy	3	2	
Hepatojejunostomy	1	–	
Choledochojejunostomy	–	1	

graphy of chest and liver, and ascitic fluid cytology.

All hepatectomy specimens were reviewed by one pathologist. Primary sclerosing cholangitis was staged according to the criteria of Ludwig *et al*[7]: stage I, cholangitis or portal hepatitis; stage II, periportal fibrosis or periportal hepatitis; stage III, septal fibrosis or bridging necrosis; stage IV, biliary cirrhosis. Patients with cholangiocarcinoma were also assessed for the tumour type, site, and spread. The bile ducts were reviewed for atypia and other foci of carcinoma.

Orthotopic liver transplantation followed standard techniques previously described[8] except for the use of a Roux-en-Y choledochojejunostomy for the biliary anastomosis. Postoperatively, the patients were treated with prednisolone and cyclosporin.

All results are expressed as mean and range of values. Statistical analysis was performed using the Wilcoxon rank sum test with $p<0·05$ being considered significant.

Results

CLINICAL FEATURES

Eleven patients (four men, seven women), mean age 40 years (range 17–48 years), received a transplant for primary sclerosing cholangitis. Four of these patients with coincidental cholangiocarcinoma were compared with the seven patients with primary sclerosing cholangitis alone. The clinical presentations of both groups are given in Table I. Three of the four patients with cholangiocarcinoma had a sudden persistent deterioration in their clinical state, with weight loss (range 6–20 kg), pruritus, and severe jaundice. The fourth patient with clinically unsuspected cholangiocarcinoma received a transplant for recurrent episodes of cholangitis and slowly progressive biliary cirrhosis. Thirteen years before transplantation a liver biopsy specimen had shown evidence of biliary cirrhosis, with cholangiography showing a dominant stricture of the common hepatic duct. Despite several drainage operations, she continued to have cholangitis. All patients with cholangitis only received a transplant due to poor quality of life secondary to end stage cirrhosis complicated by encephalopathy (two patients), variceal bleeding (four), severe ascites (two), or recurrent cholangitis (two). Apart from the mode of presentation, no great differences in clinical features existed between the two groups (Table I). Ten of the 11 patients had evidence of previous inflammatory bowel disease (ulcerative colitis seven, non-specific colitis two, Crohn's colitis one).

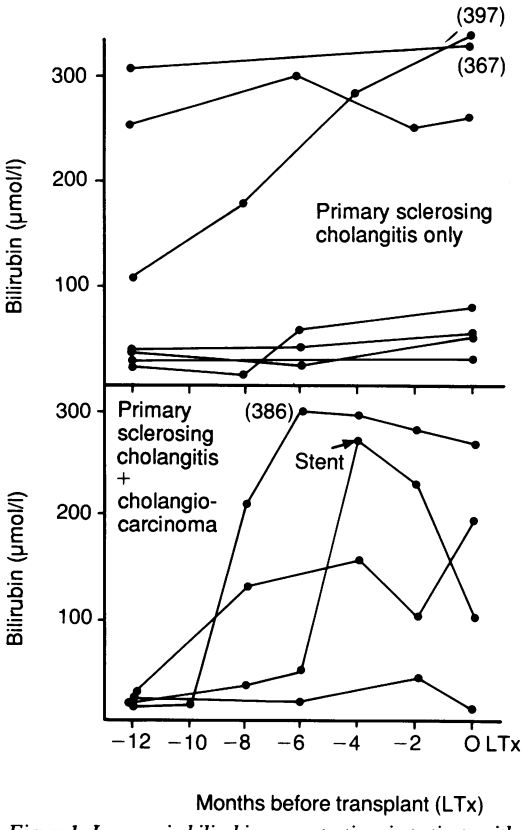

Figure 1: Increase in bilirubin concentrations in patients with primary sclerosing cholangitis only (n=7) and with coincidental cholangiocarcinoma (n=4) in the 12 months before orthotopic liver transplantation.

LABORATORY FEATURES

Laboratory test results for the two groups before transplantation are given in Table II. Patients with cholangitis alone tended to have worse indices of synthetic liver function, although due to the small numbers this was not significant. Patients with cholangiocarcinoma had a pronounced rise in bilirubin (8× *v* 2×) and alkaline phosphatase (3·5× *v* 1·2×) over the year before transplantation (Table II). The bilirubin concentrations of all patients over the year before transplantation are shown in Figure 1. Serum carcinoembryonic antigen was raised at the time of operation in two of four patients with cholangiocarcinoma (5·6, 61 μg/l, normal <5 μg/l) and

TABLE II *Laboratory features of patients with primary sclerosing cholangitis and with coincidental cholangiocarcinoma at time of transplantation (mean (range))*

	Primary sclerosing cholangitis		
	Alone	*With cholangiocarcinoma*	*p value*
Alkaline phosphatase (35–115 μmol/l)*	699 (227–1270)	781 (335–1470)	NS
Aspartate transaminase (<30 μmol/l)	166 (97–289)	92 (22–188)	NS
Bilirubin (<20 μmol/l)	178 (29–367)	143 (14–265)	NS
Albumin (35–45 g/l)	29 (16–36)	36 (33–39)	NS
Prothrombin time (n<16 s)	18 (16–20)	16 (16–17)	NS
Fibrinogen (11–25 g/l)	36 (20–52)	60 (32–95)	NS
Carcinoembryonic antigen (<5·0 μg/l)	6·2 (1·0–27·5)	17·8 (1·8–61)	NS
Bilirubin ratio†	1·99 (1·0–3·7)	8·12 (0·7–19)	0·06
Alkaline phosphatase ratio†	1·19 (0·8–2·2)	3·51 (1·1–6·4)	0·08

*Normal values in parenthesis. †Ratio: at transplant/one year before.

TABLE III *Radiological features of patients with primary sclerosing cholangitis alone and with coincidental cholangiocarcinoma*

	Primary sclerosing cholangitis	
	Alone (n=7)	*With cholangiocarcinoma (n=4)*
Dominant stricture	3	4
Pronounced ductal dilatation*	–	3
Progressive dilatation	–	2
Mass lesions	1	2
Polypoid filling defects	2	2

*Present if common bile duct >2·0 cm; left hepatic duct >1·0 cm; right hepatic duct >0·8 cm; intrahepatic ducts >0·5 cm.

in one patient without tumour (27·5 μg/l). One month after transplantation it was normal in each of the patients with tumour but was still high in the patient with benign disease (15·6 μg/l) one month before his death. In two patients tumour recurred. In one of these patients where serum was available the carcinoembryonic antigen concentration was high (155 μg/l at 21 months).

RADIOLOGY

Radiological comparison of the two groups is given in Table III. Although three of seven patients with primary sclerosing cholangitis alone and all patients with cholangiocarcinoma had a dominant stricture at cholangiography, only patients with cholangiocarcinoma developed massive ductal dilatation or progressive dilatation (Fig 2A and B).

HISTOLOGY

Hepatectomy specimens from all 11 patients showed histological evidence of primary sclerosing cholangitis. All patients with cholangitis alone had end stage biliary cirrhosis (stage IV primary sclerosing cholangitis), while patients with coincidental cholangiocarcinoma presented at an earlier stage: two had septal fibrosis only (stage III), and two early cirrhosis or cirrhosis restricted to part of the liver only (stage IV). Features universally present included focal bile duct proliferation, cholate stasis, cholestasis, and accumulation of copper associated protein at nodule or lobule margins. No granulomas were present.

Large intrahepatic bile ducts in patients with cholangiocarcinoma were appreciably dilated, although mild dilatation was also found in one patient with cholangitis alone. Intra and extrahepatic bile ducts in all 11 patients otherwise showed similar features. Large extrahepatic ducts showed mural fibrosis and chronic inflammation, whilst large intrahepatic ducts showed periductal lamellar fibrosis and atrophy of ductal epithelium. Fibrous scars occurred at sites of duct loss. The number of small intrahepatic interlobular ducts was greatly reduced. Remaining ducts were compressed by concentrically arranged fibrous tissue.

Although the diagnosis of cholangiocarcinoma was suspected on clinical and radiological grounds in three patients, histological confirmation by fine needle aspiration cytology was possible only in one patient. A second patient was diagnosed at the time of transplantation by frozen section. In two patients no evidence of tumour was found at transplantation, the diagnosis being confirmed only on microscopic examination of the total hepatectomy specimen. Absence of intra-abdominal spread was confirmed at operation before proceeding with transplantation in patients with cholangiocarcinoma.

Three patients had well or moderately differentiated sclerosing cholangiocarcinoma and one a predominantly intraductal papillary carcinoma. The tumour was located in the common hepatic duct with local invasion into both lobes of the liver in one patient, the common bile duct in one patient, common bile duct and right and left hepatic ducts in one patient, and the common bile duct, common hepatic duct, and adjacent liver in the last patient. All patients showed evidence of extensive intraneural and perineural spread affecting the cut margin of the common bile duct in three patients (including the fourth patient with a small tumour). The portal vein was microscopically involved in two patients. No patient had evidence of nodal spread. All patients had multiple areas of atypical epithelial hyperplasia (dysplasia) and

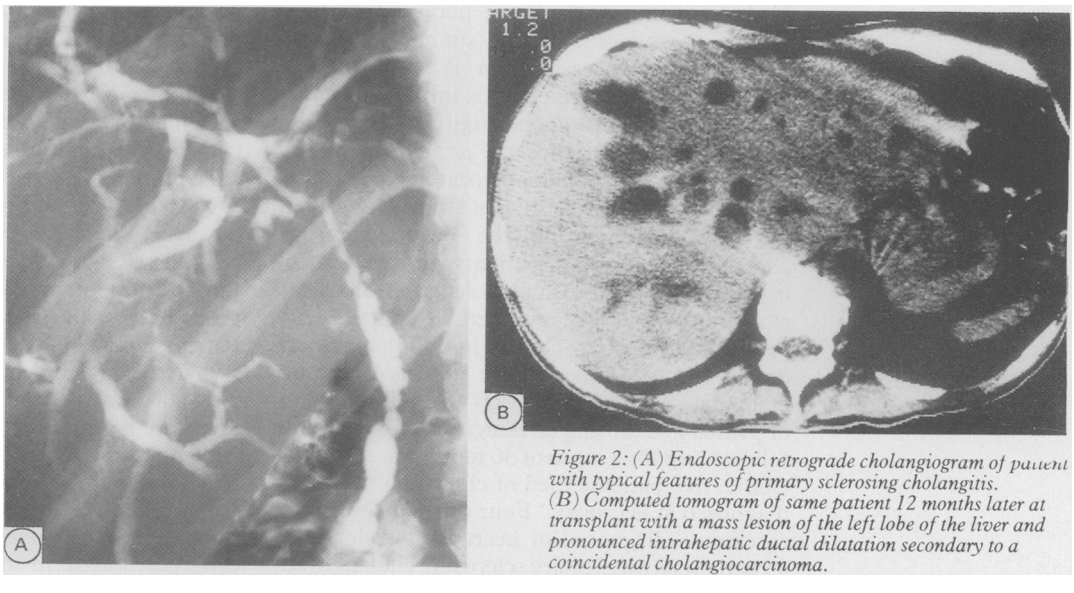

Figure 2: (A) Endoscopic retrograde cholangiogram of patient with typical features of primary sclerosing cholangitis. (B) Computed tomogram of same patient 12 months later at transplant with a mass lesion of the left lobe of the liver and pronounced intrahepatic ductal dilatation secondary to a coincidental cholangiocarcinoma.

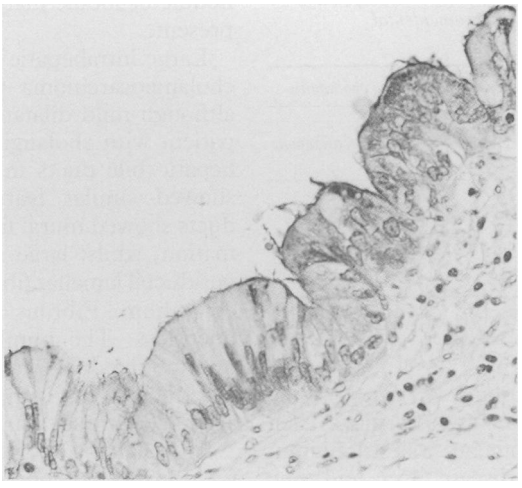

Figure 3: Transition from normal (left) to dysplastic biliary epithelium (right) in a patient with primary sclerosing cholangitis and cholangiocarcinoma. Dysplastic epithelium shows nuclear crowding and stratification and positive cytoplasmic and luminal staining for carcinoembryonic antigen. Peroxidase antiperoxidase immunoperoxidase method (original magnification ×320).

papillary carcinoma in situ at sites remote from the tumour, suggesting a multicentric origin for this tumour. None of the patients with cholangitis only had these features. Dysplastic epithelium, carcinoma in situ, and invasive carcinoma stained positively for carcinoembryonic antigen by immunoperoxidise techniques while normal epithelium was negative (Fig 3).

OUTCOME

Three of the 11 patients died of sepsis related complications within the first month of transplantation (two with primary sclerosing cholangitis only, one with primary sclerosing cholangitis and cholangiocarcinoma). The remaining five patients with cholangitis only (71%) were alive from 4–30 months after transplantation. One patient with cholangiocarcinoma died of tumour recurrence 23 months after transplantation while another patient had tumour reccurrence at 39 months. The third patient was tumour free at 14 months.

Discussion

The association of cholangiocarcinoma with ulcerative colitis has been well documented.[9–12] Mir-Madjlessi *et al*[12] calculated a relative risk of 31·3 compared with the general population. Recent careful histological studies have suggested that this association is the result of patients with ulcerative colitis initially developing primary sclerosing cholangitis.[13] Previously, by definition the diagnosis of primary sclerosing cholangitis and cholangiocarcinoma were mutually exclusive. Results of studies, however, are now documenting the development of cholangiocarcinoma in patients with well established primary sclerosing cholangitis. Chapman *et al*[3] retrospectively reviewed 29 patients with primary sclerosing cholangitis. Three of 11 deaths occurred secondary to cholangiocarcinoma developing 8–11 years after the diagnosis of primary sclerosing cholangitis. Of 68 patients followed up for a mean of 30 months at the Mayo Clinic, five patients died of cholangiocarcinoma diagnosed at necropsy.[5] Four cases of cholangiocarcinoma diagnosed at necropsy developed in 45 patients with primary sclerosing cholangitis in a study by Aadland *et al*.[4] Marsh *et al*[14] published the experience of 55 patients with primary sclerosing cholangitis undergoing orthotopic liver transplantation at the Pittsburgh centre. Five patients had evidence of occult cholangiocarcinoma at transplantation. Our results show that one third of patients who received a transplant with primary sclerosing cholangitis have coincidental cholangiocarcinoma.

Cholangiocarcinoma complicating primary sclerosing cholangitis is often difficult to diagnose due to the presence of obstructive symptoms and a distorted biliary tree. The only certain method of diagnosis is histological examination of the total hepatectomy specimen at necropsy and more recently after orthotopic liver transplantation. Despite the similarities in presentation, we were able to identify successfully three of four patients with cholangiocarcinoma before transplantation, based on sudden clinical deterioration (weight loss, jaundice, pruritus) associated with rapidly rising bilirubin and alkaline phosphatase concentrations over one year and appreciably dilated intrahepatic bile ducts. More sensitive means of diagnosing cholangiocarcinoma, however, need to be developed, as one of our patients had no clinical, laboratory, or radiological features of cholangiocarcinoma. One promising method seems to be bile brush cytology.[15] Recent reports have shown that 30–85% of tumour may be detected by this method[15] in patients with cholangiocarcinoma only. Results of studies with primary sclerosing cholangitis and cholangiocarcinoma are in progress. Immunohistochemical staining of biliary epithelium for carcinoembryonic antigen seems to discriminate between normal and neoplastic biliary epithelium in our study and others,[16 17] although the serum concentration is usually not high. This may be a useful addition to bile duct epithelial cytology to identify early carcinoma. The findings of multiple areas of dysplasia and carcinoma in situ in biliary epithelium at sites remote from the cholangiocarcinoma in the hepatectomy specimens suggest that chronic inflammation found in primary sclerosing cholangitis may stimulate premalignant change in epithelium throughout the biliary tree.[18] Detection of biliary epithelial atypia in fine needle aspirates should suggest either the presence or the future development of cholangiocarcinoma.

Histological examination of the hepatectomy specimen unequivocally showed that all patients with cholangiocarcinoma had underlying cholangitis, verifying the previous studies by Wee *et al*.[13] Patients with cholangiocarcinoma, however, tended to present for transplantation with a less severe stage of cholangitis, suggesting that the development of the cholangiocarcinoma precipitated the need for transplantation. Patients with clinical features of severe end stage primary sclerosing cholangitis, but fibrosis only and not cirrhosis on biopsy specimen, should therefore be carefully screened for complicating cholangiocarcinoma.

Although the early survival of transplanted patients with and without cholangiocarcinoma limited to the bile ducts and liver seems to be no different, longterm follow up in our study and

that of others[14 19] suggests that the majority will have tumour recurrence. This is not surprising in light of the extensive perineural and submucosal spread of the tumour, usually extending to the bile duct resection margins. Immunosuppressive treatment after transplantation may potentiate residual tumour growth.

Our policy is to give patients with primary sclerosing cholangitis with a poor quality of life and end stage liver disease a transplant. Patients suspected on clinical and radiological grounds of developing cholangiocarcinoma are aggressively investigated both before and during transplantation for evidence of tumour. Patients with definite evidence of cholangiocarcinoma are currently excluded from transplantation due to inevitable recurrence. In view of the increased risk of cholangiocarcinoma in patients with primary sclerosing cholangitis, policies may need to be modified to give such patients a transplant at an earlier stage.

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