Comment

We found that the incidence of the disease in 1966-73 was less than that in 1974-81; methods of identifying patients and retrieving information from their records and the strict criteria for confirming the diagnosis were identical during both periods, so the two periods were strictly comparable. The disease tended to be overdiagnosed clinically: 377 patients originally thought to have Crohn's disease were rejected for this study when the strict criteria were applied to clinical and diagnostic information. Incomplete identification of patients and application of these strict diagnostic criteria may, however, lead to an underestimate of the true incidence of the disease.

Crohn's disease is not rare in Northern Ireland and has a pattern and distribution similar to those in other areas of the United Kingdom. The incidence of the disease almost doubled in Northern Ireland during this study.

We thank our clinical colleagues and the pathologists who made their records available.

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Health Centre, Coleraine

J S BROWN, MB, MRCP, general practitioner

Waveney Hospital, Ballymena

W G HUMPHREYS, MD, FRCS, consultant surgeon

Queen's University, Belfast BT7 1NN

T G PARKS, MCH, FRCS, professor of surgical science

Correspondence to: Mr Humphreys.

Recurrence of hepatocellular carcinoma after liver retransplantation

Orthotopic liver transplantation is still controversial for non-resectable hepatocellular carcinoma. Survival at one year compares well with transplantation for other indications, but two year survival is significantly poorer because of late metastases, despite thorough pretransplantation screening. We report the recurrence of hepatocellular carcinoma after successful retransplantation for chronic rejection without carcinoma in the first graft.

Case report

In 1985 primary sclerosing cholangitis was diagnosed in a 26 year old white man. In June 1986 he complained of upper abdominal pain, weight loss, fever, and loss of appetite. Ultrasonic examination showed a solitary central tumour in the right lobe of the liver, confirmed by computed tomography. α Fetoprotein was not detectable. A bone scan and a radiograph of the colon were normal. Fine needle aspiration cytology showed polygonal tumour cells suggestive of hepatocellular carcinoma.

After the usual preoperative investigations the patient underwent a laparotomy with a donor liver standby, which resulted in an orthotopic liver transplantation in August 1986. Histological examination showed two tumour nodules, 4 and 2.5 cm in diameter, 2 cm apart. Immunological stainings showed α_1 antitrypsin in the tumour cells but no carcinoembryonic antigen or α fetoprotein, a presentation compatible with hepatocellular carcinoma.

Immunosuppression consisted of azathioprine 125 mg/day; prednisolone in a starting dose of 200 mg/day, which was gradually tapered, cyclophosphamide 100 mg/day for one week; and cyclosporin in doses designed to maintain blood trough concentrations of 200 ng/ml.

Five weeks after the transplantation acute rejection occurred and did not respond to an increase in the dose of corticosteroids. Chronic cholestasis developed which was attributed to chronic rejection because infectious causes were excluded and the hepatic artery anastomosis was patent. He then developed relapsing septicaemia caused by liver abscesses, which were shown by repeated arteriography to be associated with hepatic artery thrombosis. The abscesses were externally drained and longterm antibiotic treatment given. Screening for tumour recurrence was negative and we performed a retransplantation in April 1987. At

operation the resected liver showed chronic rejection but no signs of hepatocellular carcinoma. Immunosuppression as described above was used. Six weeks after retransplantation the patient was discharged with normal liver function values.

Three months after retransplantation the patient developed herpes zoster with a spiking fever. After treatment with intravenous acyclovir the zoster lesions disappeared, but the fever persisted. Liver biopsy specimens did not show rejection; repeated cultures of blood, faeces, and urine showed no pathogenic micro-organisms; cytomegalovirus infection was excluded; and arteriography showed a patent hepatic artery. Antibiotic treatment did not influence the temperature. Repeated ultrasound and computed tomography of the abdomen eventually showed hypodense areas, which were suspected of being liver abscesses. A biopsy showed recurrence of hepatocellular carcinoma. Immunological staining again showed α_1 antitrypsin in the tumour cells but no carcinoembryonic antigen or α fetoprotein. Eventually, hypercalcaemia developed associated with multiple skeletal metastases, which were confirmed by bone scanning. The patient died 14 months after his first and six months after his second transplantation.

Comment

This case raises several questions. Firstly, hepatocellular carcinoma in a patient with primary sclerosing cholangitis is unusual; nevertheless, the positive α_1 antitrypsin staining values and the histological appearances of the liver strongly support this diagnosis.

Secondly, it raises questions about patient selection. To date we have performed only three orthotopic liver transplantations among 31 patients with hepatocellular carcinoma evaluated for transplantation.¹ Originally, we considered liver transplantation to be suitable for primary hepatic malignancy, but the high recurrence rates lessened our initial enthusiasm,² although patients with fibrolamellar carcinoma may fare better than those with hepatocellular carcinoma.³ Recurrence usually occurs in the second year after transplantation. In our patient no tumour was found in the first graft after eight months, but the second liver showed recurrence within four months. Our patient had a poor prognosis because of his primary sclerosing cholangitis,⁴ but the incidental finding of the hepatocellular carcinoma would not worsen his prognosis, since Iwatsuki *et al* reported a 92% one year survival after orthotopic liver transplantation for hepatocellular carcinoma found incidentally in patients with end stage liver disease.³ Some centres, like ours, perform a diagnostic laparotomy with a donor liver standing by, proceeding to orthotopic liver transplantation only after ruling out metastases in hilar lymph nodes. This approach failed in our patient. Possibly we should not have proceeded after discovering the satellite metastasis in the recipient's own liver.

Thirdly, there is the problem of immunosuppressive therapy. The metastatic tumour growth may initially have been slower because of the longterm cyclosporin treatment,^{4,5} although this does not explain why the carcinoma recurred so rapidly in the second graft. The metastases became manifest, however, at the time they would have been expected after the first graft.

Hepatic transplantation for hepatocellular carcinoma therefore needs careful consideration, especially in patients with concomitant liver disease with a poor prognosis for orthotopic liver transplantation. Negative findings in abdominal lymph nodes and on preoperative screening do not exclude early recurrence of the tumour. Although orthotopic liver transplantation is the best palliation available for a single, incidentally found hepatocellular carcinoma, one satellite metastasis may be enough to spoil the patient's chances.

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Groningen Liver Transplantation Group, University Hospital, Oostersingel 59, 9713 EZ Groningen, The Netherlands

IDS J KLOMPMAKER, MD, consultant internist
KAREL M DE BRUIJN, MD, PHD, consultant internist
ANNETTE S H GOUW, MD, consultant pathologist
JOHANNES L BAMS, MD, consultant anaesthetist
MAARTEN J H SLOOFF, MD, PHD, consultant surgeon

Correspondence to: Dr Klompaker.