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ORIGINAL ARTICLE

Gallbladder cancer and liver transplantation

Timothy M. Schmitt, Christopher B. Hughes, Hugo Bonatti, Denise M. Harnois, Justin H. Nguyen, Rolland C. Dickson, James R. Spivey and Jeffery L. Steers

Department of Transplantation, Mayo Clinic, Jacksonville, FL, USA

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Correspondence
Christopher B. Hughes, Department of Surgery, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, USA. Tel.: (904) 953-2000; fax: (904) 953-5874; e-mail: hughes.christopher@mayo.edu

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Summary

Gallbladder cancer is the fifth most common malignancy of the gastrointestinal tract. Gallbladder cancer is found incidentally at the time of cholecystectomy in 0.35% of patients. Two previous isolated case reports of incidentally found gallbladder cancer in hepatectomy specimens following liver transplantation (LT) showed no adverse outcomes. We reviewed the outcome of four patients. Three patients had end-stage liver disease secondary to primary sclerosing cholangitis and one patient had cryptogenic cirrhosis. Gallbladder cancer was removed at cholecystectomy in one patient 11 months prior to transplant. One patient had suspected gallbladder cancer prior to LT by ultrasound and CT imaging, as well as a rising CA 19-9. The other two patients had incidentally identified gallbladder cancer. Median follow-up was 30 months. There has been no evidence of recurrence and patient survival was 100%. Early gallbladder cancer is not a contraindication for LT, however further follow-up is needed.

Introduction

Cancer of the gallbladder is an aggressive malignancy and with the exception of those found incidentally at elective cholecystectomy the prognosis is dismal. Gallbladder cancer is the fifth most common malignancies of the gastrointestinal tract [1]. Gallbladder cancer will be encountered approximately 0.35% of the time on routine cholecystectomy [2]. Primary sclerosing cholangitis (PSC) is a chronic cholestatic disorder, typically affecting young patients with inflammatory bowel disease (IBD) such as ulcerative colitis or Crohn's disease. Patients with PSC have and increased incidence of cholangiocarcinoma, which has been demonstrated on studies of hepatectomy specimens following transplantation [3–5]. Typically gallbladder cancer presents late in its course, is unresectable and fatal. Early gallbladder cancer however, cancer confined to the mucosa (T1a) or muscularis (T1b), has an 80–100% cure rate when treated with simple cholecystectomy [6,7]. A recent history of a variety of malignancies such as colonic cancer, breast cancer or lymphomas and leukaemias are considered contraindication for liver transplantation (LT). LT for early stages of hepatic malignancies including hepatocellular carcinoma and cholangiocarcinoma as well as some secondary malignancies such as neuroendocrine tumours reveal acceptable results. Isolated reports of incidentally found gallbladder cancer in hepatectomy specimens and LT following treated early gallbladder cancer show no adverse outcomes [8,9].

We present four cases of liver transplantation in patients with gallbladder cancer. The first patient underwent cholecystectomy with early gallbladder cancer prior to LT, and the second patient was transplanted with suspected cancer, which was confirmed in the explanted liver. The third patient, transplanted for PSC and hepatocellular carcinoma, was found to have an incidental gallbladder carcinoma. The fourth patient, transplanted for cryptogenic cirrhosis, was found to have a low-grade stromal tumour of the gallbladder.

Patients

Case 1

The first patient is a 51-year-old male with PSC with a history of ulcerative colitis that was relatively inactive. During follow-up on ultrasound he was noted to have a nodular abnormality of 1 cm in diameter within the wall

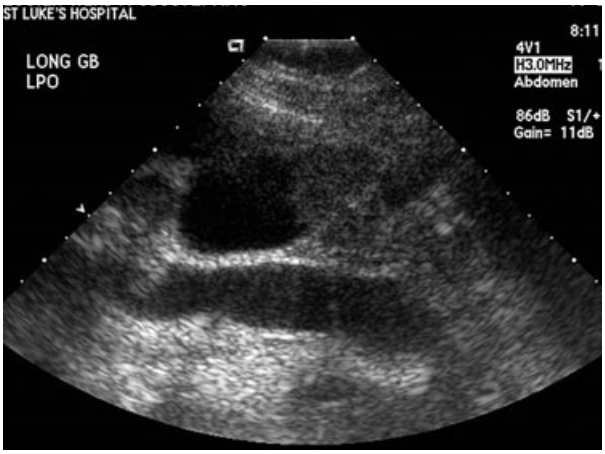

Figure 1 Ultrasound showing hyper-echoic lesion in the gallbladder.

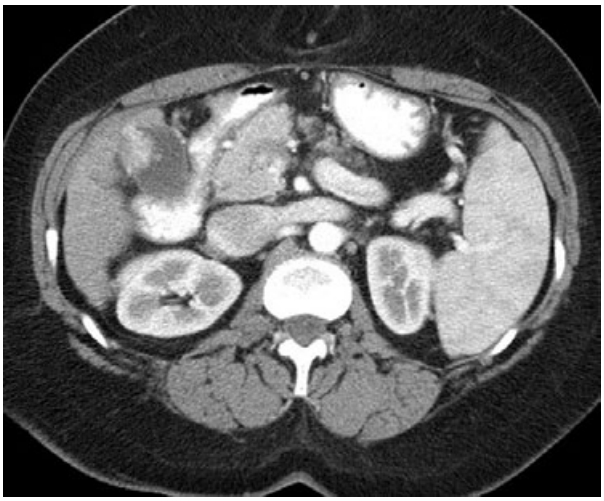

Figure 2 CT scan of the abdomen showing nodular mass in the gallbladder.

of the gallbladder. Subsequent cholecystectomy revealed a T2 N0 M0 adenocarcinoma of the gallbladder. He received postoperative chemotherapy with 5-FU and radiation therapy. Subsequently his liver progressively failed and he was transplanted 11 months following his cholecystectomy. Preoperative evaluation excluded recurrence of the cancer, which was confirmed during hepatectomy prior to implantation of the graft. His postoperative course was uneventful and the patient at present showed no evidence of tumour recurrence 42 months following LT.

Case 2

The second patient is a 47-year-old female with end-stage liver disease secondary to PSC. She had undergone a previous total colectomy and ileostomy for IBD. Routine ultrasound noted gallbladder sludge versus polyp 5 months prior to transplantation (Fig. 1). Follow-up ultrasound was recommended. She did not have symptoms of cholecystitis. Follow-up ultrasound again demonstrated the presence of a possible polyp in the gallbladder. CT scan (Fig. 2) and endoscopy retrograde cholangiopancreatography were performed. Both confirmed the presence of a mass within the gallbladder. CA 19-9 at the initial ultrasound time was mildly elevated to 66 U/ml (normal range 0–32 U/ml). When CA 19-9 during follow-up after 6 months rose to 308 U/ml, the decision was made to proceed to LT. At this time her liver function had been significantly worsening. At the time of LT, external inspection of the gallbladder revealed no evidence of tumour penetration or fixation. A hilar lymph node dissection was performed and three negative nodes were found. LT was subsequently completed without complication. Following LT, hepatic artery thrombosis developed which required retransplantation, which was carried out successfully. No further anti-tumour treatment including chemotherapy or radiation was commenced. Within 2 weeks following LT, CA 19-9 normalized to 21.9 U/ml and remained so during follow-up. Thirty months following transplantation there was no evidence of recurrence by imaging and normal CA 19-9.

Case 3

The third patient is a 61-year-old male with a history of Crohn's disease and end-stage liver disease secondary to PSC, complicated with hepatocellular carcinoma. He was chemoembolized 3 months prior to transplantation. Preoperative CA 19-9 was 60.5 U/ml. The pathological examination of the explanted liver revealed multiple areas of hepatocellular carcinoma as well as a $2.5 \times 2.5 \times 1.5$ cm T2 lesion in the gallbladder. Hiliar lymph nodes were negative for tumour. Postoperatively his course was complicated by bleeding which required exploratory laparotomy. Following recovery he underwent chemotherapy with cisplatin and gemcitabine for the hepatocellular carcinoma. Following transplant his CA 19-9 dropped to 15 U/ml, and 22 months later to 5 U/ml. He had no evidence of recurrence 22 months following transplant.

Case 4

The fourth patient is a 64-year-old male with cryptogenic cirrhosis. Preoperative CA 19-9 was 17.4 U/ml. Pathological examination of the explanted liver revealed a low-grade stromal tumour of the gallbladder. The tumour arose from the serosa of the gallbladder and involved the cystic duct, but did not involve the liver or hilar lymph nodes. The maximum diameter of the tumour was 5 cm

and the mitotic count was <1 per 50/high power fields. Immunohistochemical staining was negative for c-Kit. Postoperatively the patient did well. He had an uncomplicated course and has no evidence of recurrence 28 months following surgery.

Discussion

Gallbladder cancer is found incidentally in approximately 0.35% of cholecystectomy specimens [2]. Curative resection is possible in 20–40% of all cases [10]. Depth of invasion as well as lymph node status has been shown to be the primary prognostic indicators of survival. Early gallbladder cancer is typically asymptomatic and found either by ultrasound or incidentally at the time of cholecystectomy. Tumour that is contained within the gallbladder at the time of surgery (T1 and T2) with no lymph node invasion is referred to as early gallbladder cancer. Simple cholecystectomy is recommended for T1 and T2 lesions achieving 5-year survival rates between 44% and 100% [6,7,11]. PSC is a chronic cholestatic liver disease with unknown cause that is often associated with IBD. The usual course is progressive in nature and does not stop with the removal of the colitis. Patients with PSC have an increased incidence of hepatobilary malignancy, most commonly intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma and gallbladder carcinoma. Isolated reports of liver transplantation in patients with both previously diagnosed gallbladder cancer and cancer found on the explanted liver have reported no adverse outcomes [8,9].

Transplantation for PSC accounts for a significant percentage of the total liver transplanted until at present. Most centres report high patient and allograft survival. However there is also a reported incidence of 10–36% incidence of primary hepatobiliary malignancy at the time of transplant [3–5]. In a recent review of patients transplanted with PSC, the incidence of primary hepatobiliary malignancy, all cholangiocarcinoma, was 11% [12]. In our own centre within a series of 467 consecutive LT performed between March 1998 and December 2001, a total of 33 transplants (7.1%) in 26 patients were carried out for PSC. None of these patients was co-diagnosed having cholangiocellular carcinoma. The two cholangiocarcinomas we transplanted during this time period were not associated with PSC. PSC patients undergoing transplant with incidentally found cholangiocarcinoma had similar 1-, 2- and 5-year survival when compared with PSC patients transplanted without carcinoma [12]. Whether or not this experience can be translated to early or incidental gallbladder cancer in unknown.

Can diagnosis be made in a timely manner in order to surgically treat early cancer in patients with PCS who would not otherwise be transplanted in a timely fashion? Approximately one-third of the diagnoses have been made using ultrasound in a Japanese series [13]. However with an increased incidence of gallstones this number is far smaller in North American and European reports [14]. Tumour markers can also be used to help predict cancer. In a report from the Mayo Clinic in Rochester, CA 19-9 is elevated in 89% of patients with PSC and cholangiocarcinoma versus only 14% of patients who had an elevated CA 19-9 with only PSC [15]. When levels are greater than 100 U/ml, the sensitivity was 89% and specificity was 86%. However Mount Sinai reported 48% of patients with PSC without cancer had an elevated CA 19-9 [16].

Gallbladder cancer has an incidence of 0.35%. This would likely translate to the incidence found at transplant. Patients with PSC have an increased incidence of hepatobiliary cancer, mostly cholangiocarcinoma. Abnormalities found on ultrasound or elevated CA 19-9 without evidence of cholangiocarcinoma might lead to the suspicion of gallbladder cancer. Further follow-up is needed to determine if LT with early gallbladder cancer in the explanted liver will lead to adverse outcomes. Gallbladder cancer should not be considered a contraindication against LT if removed at an early stage. However long-term follow-up in these patients will also be necessary. Preoperative ultrasound and CA 19-9 should be followed in patients with PSC to monitor for their increased risk of cholangiocarcinomas.

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