Case Report

Hepatocellular carcinoma secondary to cholecystectomy: a one in a million chance

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Background

Cholecystectomy is a common procedure and its complications are well documented.

Case Outline

A 63-year-old female sustained a bile duct injury during cholecystectomy requiring choledochoduodenostomy. She subsequently developed secondary biliary cirrhosis and ultimately required orthotopic liver transplantation. A focus of hepatocellular carcinoma was discovered within her liver.

Discussion

This case represents the first documented case of hepatocellular carcinoma as a late complication of cholecystectomy. The risk of this occurring can be estimated at 1:1,140,000 (range 1:11,000 to 1:120,000,000).

Key Words

cholecystectomy, choledochoduodenostomy, complications, hepatocellular carcinoma/hepatoma, liver transplantation, secondary biliary cirrhosis

Introduction

Cholecystectomy is a widely practised and usually very safe procedure, although its potential complications are well recognised and widely reported [1]. Neoplasms developing as a result of cholecystectomy, or any other routine surgical procedure, are rare in the literature. We report a case of hepatocellular carcinoma (HCC) directly associated with a preceding cholecystectomy.

Case report

In December 1992 a 63-year-old non-smoking woman was referred to the Scottish Liver Transplant Unit. She had undergone cholecystectomy for cholelithiasis 19 years previously. The operation had been complicated by transection of the common bile duct and was followed three weeks later by choledochoduodenostomy. She subsequently had intermittent episodes of cholangitis and was extensively reinvestigated five years later. Ultrasonography revealed parenchymal liver disease and splenomegaly. Liver biopsy showed secondary biliary cirrhosis with no excess of iron, copper or alpha-1 antitrypsin; cholescintigram was normal with no evidence of biliary obstruction. An upper gastrointestinal endoscopy revealed early varices.

Fifteen years after the original operation, she presented with haemorrhage from her varices and required multiple blood transfusions. She was managed by injection sclerotherapy but subsequently required oesophageal dilatation for stricturing caused by the sclerotherapy.

When she was referred to our unit four years later, she had a two-year history of intermittent episodes of encephalopathy. Her liver function tests were deranged: serum bilirubin 34 μmol/l (normal 2–17), alkaline phosphatase 220 U/l (40–125), gamma-glutamyl transferase 293 U/l (5–35), albumin 30g/l (36–47), prothrombin time 16 seconds (control 12 seconds). Hepatitis B and C virus serology and serological measurements of anti-nuclear factor, anti-mitochondrial antibody and anti-smooth muscle antibody were all negative. Serum alpha-fetoprotein was 4 iu/l (normal 2–6). A barium meal demonstrated stenosis of both the duodenum and bile duct at the site of the anastomosis and reflux of barium into the biliary system with evidence of a dilated intrahepatic biliary tree. Ultrasound scan and hepatic angiogram revealed no evidence of any focal parenchymal hepatic lesions. The angiogram showed portal hypertension and reversal of portal venous flow. In view of her impaired hepatic function, orthotopic liver transplantation was undertaken in March 1993.

Within the resected liver was a 1.5 cm nodule of moderately differentiated, multinodular, unencapsulated

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hepatocellular carcinoma. The tumour cells did not stain for hepatitis B surface antigen but were positive for alpha-1 antitrypsin. There was no evidence of vascular, lymphatic or perineural invasion. The remainder of the liver showed well established secondary biliary micronodular cirrhosis with a number of macronodules.

Initial postoperative recovery was marked by severe acute graft rejection, which responded to corticosteroids, and a bile leak, which required refashioning of the biliary anastomosis. She was discharged 47 days after the transplantation, but developed late stenosis of the biliary-enteric anastomosis which required surgical revision four months later. She then developed chronic graft rejection necessitating a second transplantation six months after the first. Postoperative hepatic artery thrombosis led to an emergency retransplantation procedure one week later, which failed because of acute rejection. The patient died seven months after the initial liver transplantation.

Discussion

Bile duct injury is a major potential complication of cholecystectomy, with a reported incidence of 0.07%–0.9% [1,2]. Whether this figure is higher in the era of laparoscopic surgery remains controversial. Bile duct injuries may be detected and corrected intraoperatively, in the early postoperative period, or they may present many years after the operation [3]. Late bile duct stricturing may lead to secondary biliary cirrhosis in 6–30% of cases [3,4]. Although cirrhosis as a result of a previous bile duct injury requiring liver transplantation has been reported [5], development of a hepatocellular carcinoma (HCC) in association with cirrhosis due to a bile duct injury has not.

It is well recognised that hepatic cirrhosis due to alcohol abuse, iron overload (haemochromatosis) or copper overload (Wilson's disease) is a risk factor for the development of HCC, even though in these diseases the ethanol, iron, and copper that cause the cirrhosis are not currently thought to be directly carcinogenic. Approximately 70% of primary HCC arises in cirrhotic livers, and it is currently hypothesised that the regeneration of cells associated with cirrhosis may be a tumourgenic process. DNA synthesis is accelerated in regenerating nodules, and this may result in increased rearrangement of oncogenic sequences within the chromosomes. Macronodular cirrhosis is thought to be more likely to cause HCC than micronodular cirrhosis due to the higher level of regenerative activity [6]. Hepatocyte dysplasia has been described in association with cirrhosis of various aetiologies [7], but it remains uncertain whether these dysplastic hepatocytes are indeed premalignant [8].

In the present case, it is important to note that all other recognised risk factors for cirrhosis or HCC have been excluded. The patient had no history of alcohol abuse, and other possible causes of cirrhosis including haemochromatosis, alpha-1 anti-trypsin deficiency, Wilson's disease, autoimmune liver disease and viral hepatitis were excluded. Aside from cirrhosis, hepatitis B virus infection and aflatoxin exposure are the major independent risk factors for development of HCC. Hepatitis B has been excluded and the patient was unlikely to have had appreciable exposure to occupational or dietary aflatoxin.

We therefore believe that there is a causative relationship between the cholecystectomy and the occurrence of a HCC in this patient. The sequence of events was an iatrogenic bile duct injury during cholecystectomy, which was repaired by a choledochoduodenostomy. Subsequent stenosis of the biliary-enteric anastomosis resulted in episodes of cholangitis and secondary biliary cirrhosis. HCC developed on this cirrhotic background.

The overall risk of developing HCC as a result of cholecystectomy can be estimated as follows. The frequency of bile duct injury due to cholecystectomy is in the range 0.07%–0.9% [1,2,9,10]. Appropriate surgical intervention usually leads to successful repair of bile duct injuries, but 2–15% of patients will have recurrent complications such as anastomotic stricturing and cholangitis [11,12], and of these 6–30% will develop cirrhosis [3,4]. The frequency of progression from cirrhosis to HCC in hepatitis B and C virus negative patients has been reported to be 1.0–22.6% [13,14,15]. Taking the mid-points of these ranges of figures would give an overall risk of 1:1,140,000 (range 1:11,000 to 1:120,000,000) for developing HCC as a result of cholecystectomy. As with most neoplastic diseases, tumourgenesis here is likely to be a multifactorial process and other as yet undefined aetiological factors might also be involved.

This case highlights the rare possibility of developing a malignancy as a result of a very frequent routine surgical procedure. It should be emphasised that the recommended repair following bile duct injury is Roux-en-Y hepaticojejunostomy with careful follow-up to ensure there is no evidence of late anastomotic stenosis or secondary biliary cirrhosis.

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