Hepatobiliary Scintigraphy in Patients Receiving Hepatic Artery Infusion Chemotherapy

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Hepatic artery infusion chemotherapy is used in the treatment of certain selected hepatic tumors, especially metastatic adenocarcinoma of the colon. Chemical cholecystitis has been recognized recently as a complication of hepatic artery infusion chemotherapy. We performed hepatobiliary scans on ten patients receiving hepatic artery infusion chemotherapy. All ten patients had abnormal hepatobiliary scintigraphy. We present case reports of three patients with abnormal hepatobiliary scans who have required cholecystectomy for symptoms of chemical cholecystitis to illustrate the clinical, scintigraphic, and pathologic findings in these patients.

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Chemical cholecystitis has been recognized as a complication of hepatic artery infusion chemotherapy (1). We have performed hepatobiliary scintigraphy on ten patients who had received regional hepatic artery infusion chemotherapy. All ten patients had abnormal hepatobiliary scintigraphy with nonvisualization of the gallbladder at 1 hr. We present three patients with severe upper abdominal pain and abnormal hepatobiliary scintigraphy after hepatic artery infusion chemotherapy. These three patients required cholecystectomy which demonstrated pathological changes consistent with chemical cholecystitis.

CASE REPORTS

Case 1

A 52-yr-old male underwent a right hemicolectomy and operative placement of a hepatic artery catheter and subcutaneous infusion pump for treatment of a moderately differentiated adenocarcinoma of the ascending colon with biopsy evidence of metastases in the liver. Correct placement of the hepatic artery catheter was confirmed by intraoperative hepatic perfusion scintigraphy (2). The liver function tests were total bilirubin 0.2 mg/dl, SGOT 18 U/l, SGPT 24 U/l. The CEA was 190 IU/ml. The patient was started on hepatic artery infusion chemotherapy with 5-fluorodeoxyuridine (5-FUDR) at the rate of 0.225 mg/kg/day for 14 days, followed by saline infusion for 14 days. The patient underwent four such treatments. When the patient returned for the fifth treatment, he complained of significant right upper quadrant pain. At that time, his liver function tests were total bilirubin 0.2 mg/dl, SGOT 272 U/l, and SGPT 433 U/l. The patient was thought to have chemical hepatitis and the hepatic artery 5-FUDR dosage was decreased to 0.135 mg/kg/day. He received one such treatment. One month later, his liver function tests were total bilirubin 0.2 mg/dl, SGOT 26 U/l, and SGPT 26 U/l. His hepatic artery 5-FUDR dosage was further reduced to 0.09 mg/kg/day, and he received two courses at this reduced dosage with clinical improvement in the right upper quadrant pain.

After the seventh course of intraarterial chemotherapy, the patient experienced severe right upper quadrant pain and was admitted to the hospital. The liver function tests were total bilirubin 0.2 mg/dl, SGOT 31 U/l, and SGPT 40 U/l. The CEA had decreased to 33 IU/ml. Hepatobiliary scintigraphy (3) demonstrated normal visualization of the liver, visualization of the common bile duct at 20 min, and visualization of the small bowel at 1 hr. There was nonvisualization of the gall-bladder through 4 hr (Fig. 1).

The patient underwent an exploratory laparotomy and a cholecystectomy was performed. Pathological examination of the gallbladder showed the wall thickened by fibromuscular tissue with edema, congestion, scarring, and fibrosis. The epithelium showed atypia with enlarged, irregular pleomorphic nuclei. Scattered fibroblasts in the stroma also showed en-

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FIGURE 1

Case 1: Hepatobiliary scan following 4.5 mCi (166 MBq) (4.5 mCi) [^{99m}Tc]disofenin shows excellent visualization of bile duct and small bowel at 60 min (A). There is nonvisualization of gallbladder at 4 hr (B)

larged, somewhat irregular atypical nuclei. The findings suggested chronic cholecystitis secondary to chemotherapy (Fig. 2).

Postoperatively, the patient had marked improvement in the right upper quadrant pain. He had one additional course of hepatic artery infusion chemotherapy before pulmonary metastases were discovered. He was started on systemic chemotherapy and no further hepatic artery chemotherapy was administered.

Case 2

A 52-yr-old male was admitted with a distal colon obstruction and had a left hemicolectomy for a grade 2 adenocarcinoma of the left colon with 4/31 regional lymph nodes positive for carcinoma. Liver biopsy showed metastatic adenocarcinoma and a hepatic artery catheter and subcutaneous infusion pump were implanted. Correct placement of the hepatic artery catheter was confirmed by intraoperative hepatic perfusion scintigraphy (2). The patient was started on hepatic artery infusion chemotherapy with 5-FUDR at a dose of 0.3 mg/ kg/day. After the first dose, the liver function test rose to total bilirubin 10.1 mg/dl, SGOT 173 U/l, and SGPT 239 U/l. The second hepatic artery infusion of 5-FUDR was reduce to 0.22 mg/kg/day, but the total bilirubin rose to 22.2 mg/dl. Hepatic artery infusion chemotherapy was stopped for 4 mo and the total bilirubin decreased to 1.1 mg/dl. The liver function test further decreased to total bilirubin 0.9 mg/dl, SGOT 50 U/l, and SGPT 58 U/l. Hepatic artery infusion of 5-FUDR was restarted at a dose of 0.13 mg/kg/day. The patient received five treatments at monthly intervals at this dosage. The patient experienced increasingly severe abdominal pain and no further intraarterial chemotherapy was administered. Over the next 4 mo, the liver function test increased to total bilirubin 9.1 mg/dl, SGOT 278 U/l, and SGPT 233 U/l. Hepatobiliary scintigraphy (3) demonstrated good visualization of the liver, activity in the common bile duct by 30 min, and activity in the small bowel by 1 hr.

At laparotomy, there was marked sclerosis of the gallbladder bed and the area of the common bile duct. Cholecystectomy was performed and the gallbladder wall showed areas of fibrosis and focal infiltrates by lymphocytes. The pathological diagnosis was chronic cholecystitis.

Case 3

A 50-yr-old male was admitted with a 3-wk history of abdominal pain and a 3-day history of a palpable midepigastric mass. Laparotomy and liver biopsy showed hepatocellular carcinoma. A hepatic artery catheter and subcutaneous infusion pump were placed surgically. Correct placement of the hepatic artery catheter was confirmed by intraoperative hepatic perfusion scintigraphy (2). The patient received hepatic artery infusion chemotherapy consisting of 5-FUDR 0.19 mg/kg/day by infusion pump and doxorubicin hydrochloride, 25 mg, by intraarterial bolus at monthly intervals for 13 mo. He received mitomycin-C 10 mg by intraarterial bolus during every other treatment. During the first 4 mo of treatment, the CEA decreased from 244 IU/ml to none detected. The patient continued to do very well until after the next to the last hepatic artery infusion chemotherapy administration when he developed increasingly severe abdominal pain. Upper GI series and endoscopy were negative for ulcer. Liver function tests were total bilirubin 0.2 mg/dl, SGOT 38 U/l, and SGPT 28 U/l. Hepatobiliary scintigraphy (3) demonstrated good visualization of the liver, visualization of the common bile duct by



FIGURE 2

Case 1: Photomicrograph of gallbladder wall shows areas of hemorrhagic necrosis of mucosa, thickening of muscularis, and fibrosis and congestion of the serosa, consistent with chemical cholecystitis

20 min, and activity in the small bowel by 1 hr. There was nonvisualization of the gallbladder at 4 hr.

Laparotomy demonstrated marked fibrosis and thickening of the wall of the gallbladder. The cystic duct was completely obliterated, and the gallbladder contained clear mucinous fluid, with no evidence of bile. There was also marked fibrosis surrounding the common hepatic duct and portal triad. Pathological examination of the gallbladder revealed that the mucosa showed areas of hemorrhagic necrosis. The muscularis was thickened and the serosa was fibrosed and congested. The pathological diagnosis was gallbladder showing hemorrhagic necrosis, consistent with chemical cholecystitis.

The patient reported dramatic improvement of the abdominal pain following the operative procedure. There has been no increased in the size of the liver tumor by computed tomography, the CEA has remained undetectable, and the patient has not received additional intraarterial chemotherapy.

DISCUSSION

Hepatic artery infusion chemotherapy has been used for several years in the treatment of hepatic tumors, especially metastatic carcinoma of the colon. In 1979, Ensminger and Niederhuber (4) adapted an implantable continuous perfusion system to deliver regional chemotherapy to the liver. There is no well-designed randomized prospective trial comparing systemic chemotherapy and hepatic artery infusion chemotherapy. In spite of this, regional chemotherapy with a surgically implanted hepatic artery catheter and pump has continued to be the treatment of choice in several institutions for certain selected patients with both primary and metastatic tumors of the liver (5,6).

Complications including mild gastritis, ulceration, and icteric and anicteric chemical hepatitis were reported from the early experience with surgically implanted hepatic artery infusion systems (7). These complications may result from the perfusion of the stomach, duodenum, or pancreas during regional hepatic artery infusion chemotherapy (8). The blood supply of the gallbladder has been well described, and in the vast majority of patients receiving hepatic artery infusion chemotherapy, the gallbladder will be included in the region perfused (1). However, chemical cholecystitis was not identified in the early studies and elective cholecystectomy was not recommended (7).

In 1983, Carrasco et al. (1) reported four cases of chemical cholecystitis associated with hepatic artery infusion chemotherapy, two of which required cholecystectomy. In their four patients, the diagnosis was made by ultrasonography or angiography and hepatobiliary scintigraphy was not reported.

We present three patients who developed severe right upper quadrant pain after hepatic artery infusion chemotherapy. Each of these three patients had abnormal hepatobiliary scintigraphy and operative evidence of cholecystitis, most likely due to intraarterial chemotherapy. In our study, we identified scintigraphic evidence of gallbladder dysfunction, presumably due to chemical cholecystitis, in ten of ten patients receiving hepatic artery infusion chemotherapy. Our data suggest that scintigraphic evidence of cholecystitis is very common, if not uniformly present during hepatic artery infusion chemotherapy.

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