Fatal Bile Duct Necrosis: A Rare Complication of Transcatheter Arterial Chemoembolization in a Patient with Endocrine Hepatic Metastasis

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Abstract
We report the first case of fatal bile duct necrosis following transcatheter arterial chemoembolization (TACE) in a 58-year-old woman. The patient underwent two TACEs to treat hepatic metastases from an ileal endocrine tumor. Persistent cholestasis occurred after the second procedure, leading to the diagnosis of bile duct necrosis confirmed by liver biopsy. The patient died of liver failure with encephalopathy six months after the second TACE. Even though this complication is very rare, physicians should consider this diagnosis in patients who develop chronic, marked cholestasis following a TACE procedure.

Case Report
A 58-year-old woman was operated on in February 2005 for an ileal stenosis revealed by an occlusion. She had no past personal or familial medical history. A 15 cm resection of the ileum and colon was performed followed by an ileocolic anastomosis. Light microscopy analysis showed a well-differentiated endocrine tumor of the ileum with extension into the appendix and the ileocecal valve. The proliferation index Ki-67 was 4%. One out of seven lymph nodes analyzed was metastasized. There was tumor extension in the fat tissue surrounding the tumor. No vascular or perinervous sheath tumor embolism was noticed. The surgical margins were negative.
A thoracoabdominal CT scan and a somatostatin receptor scintigraphy with indium-111-labeled octreotide performed postoperatively were normal. Serum chromogranin A levels were 1.2N (N: upper limit of normal value) and urinary excretion of 5-hydroxyindoleacetic acid was normal. Since tumor resection was complete, simple observation was decided.

In January 2006, flushing and diarrhea appeared. Chromogranin A was 8N and hepatic enzymes were normal. CT scan showed multiple and bilateral liver metastases, the largest measuring 2 cm, with a global involvement of the liver of less than 50% (fig. 1). No other tumor sites were identified on imaging. An anatomical variant with three hepatic arteries was noticed on the arterial phase of the CT scan. According to Couinaud’s classification [1], the left hepatic artery vascularized segments II and III, the middle, the caudate lobe and segment IV, and the right artery, segments V to VIII. Since curative hepatic surgery was impossible, transcatheter arterial chemoembolization (TACE) was decided to treat symptoms and control tumor growth.

The first TACE was performed in March 2006. It included selective injection of a mixture of streptozocin and iodized oil followed by gelatine sponge particles in the three hepatic arteries. Antibiotic prophylaxis was administered (ceftriaxone and metronidazole) and the right femoral artery was infused with a 5 F catheter under general anesthesia. Selective catheterization of each arterial branch was performed to inject the mixture (left: 7 ml, middle: 5 ml, right: 10 ml). Although there were no complications during the procedure, clinical tolerance was poor with asthenia and pain requiring opiates. Four days after TACE, liver tests were abnormal as follows: aspartate aminotransferase (AST) 2N, alanine aminotransferase (ALT) 4N, alkaline phosphatase (ALP) 1.4N, gammaglutamyl transpeptidase (GGT) 6N, total bilirubin (TB) 49 μmol/l (conjugated bilirubin 23 μmol/l). Three months later, GGT and ALP serum levels remained abnormal (13N and 3N, respectively). AST and ALT were normal. The bile ducts were not dilated on abdominal ultrasound. There was an objective response in the tumor on CT scan and intense staining of metastases with lipiodol (fig. 2). A second TACE was performed in June 2006 with the same procedure. Five days later, the patient developed jaundice. Liver tests were as follows: TB 100 μmol/l, ALP 3.3N, GGT 18N, AST 67N, ALT 47N. Prothrombin time (PT) was 100%. An abdominal ultrasound showed no bile duct dilatation, venous thrombosis or abscess. Serology for hepatitis A, B, C, herpes, Epstein-Barr virus, cytomegalovirus and HIV was negative. Anti-nuclear, anti-smooth muscle, anti-LKM1 and anti-mitochondrial antibodies were absent. Copper and ceruloplasmin serum levels were normal. There were no signs of hemochromatosis or drug-induced hepatitis. Biochemical analysis two weeks later showed: ALP 4N, GGT 14N, AST 3N, ALT 4N, TB 81 μmol/l and PT 100%. Three months after the procedure, the patient was still tired, with no flushing or diarrhea. TB was at 67 μmol/l, GGT 22N, APL 4.5N, PT 76%. On CT scan and magnetic resonance imaging of the liver, metastases were stable and there was no bile duct enlargement. A liver biopsy was performed. Histological analysis showed distorted interlobular bile ducts with intrahepatocytic and canalicular cholestasis combined with ductular proliferation suggesting biliary ischemic necrosis (fig. 3).

As the liver metastases remained stable and since no biliary drainage was possible, follow-up was decided. In January 2007, the patient’s condition worsened (OMS index 3) and she lost 6 kg. Cholestasis increased (TB 213 μmol/l). A new CT scan showed minor dilatation of the biliary tract. Transcutaneous drainage was attempted to relieve what appeared to be extrahepatic biliary duct stenosis causing worsening of intrahepatic bile stasis. However, clinical and biochemical features worsened rapidly and hepatic insufficiency occurred with ascites, a decrease in PT (40%) and factor V (52%) (fig. 4). Histological examination of a second liver biopsy showed vanishing intralobular bile ducts and extensive portal fibrosis, more severe than at first biopsy. Because of the severe liver failure and the stabilized tumor, liver transplantation was decided. However, liver failure rapidly worsened and the patient died while on the waiting list.

Discussion

This is the first report describing TACE complicated by fatal hepatic insufficiency following severe bile duct necrosis in a patient without cirrhosis treated for metastases of an ileal endocrine tumor. This is the only death that has occurred in our center in patients treated by TACE (230 TACEs/year).

TACE is a widely accepted procedure for the treatment of liver tumors [2] and is especially effective in patients with liver metastases from endocrine tumors with a mean
objective response rate of 50% (37–85%) [2–5]. It is a valuable option as a first-line, non-surgical treatment particularly when the primary tumor has been surgically removed and metastases are confined to the liver [2–4]. Theoretically, the combination of intraarterial infusion of a chemotherapeutic agent and embolization of the arterial supply of the tumor produces direct ischemia. In addition, it increases transit time through the tumor vessel, thus increasing the amount of time the drug is in contact with neoplastic cells [6]. The main contraindications are portal vein thrombosis and liver insufficiency [7]. Previous pancreaticoduodenectomy is also a contraindication because of postoperative vascular changes and the risk of abscess secondary to bacterial contamination through the bilioenteric anastomosis [8].

The occurrence of fever (30–60%), epigastralgia (50–60%) and increased transaminases (100%) are often noted [9]. Severe complications, i.e. cholecystitis, gastric ulcers, intrahepatic biloma, cholangitis, abscess, sepsis, or acute hepatic failure occur in less than 5% of patients [10–13]. In a report of 2,012 TACE procedures, Xia and al. [14] described common hepatic artery occlusion (n = 40) but also spontaneous rupture of the tumor (n = 3), abscess (n = 3), femoral nerve injury (n = 3), duodenal perforation (n = 1), pulmonary embolism (n = 1), spasm of the hepatic artery (n = 1), bilioma (n = 1) and acute renal failure (n = 1). Only one case of fatal hepatic failure was reported one week after a TACE procedure in a patient with hepatocellular carcinoma and cirrhosis (no autopsy) [12]. Several case reports have been published in the last two decades reporting cholangitis with fibrosis on histological specimens after TACE for colorectal metastases or hepatocellular carcinoma. The diagnosis was based on a liver biopsy performed to explore persistent cholestasis after the procedure [15–17]. Tarazov et al. [10] described three cases of ischemic complications with bile duct necrosis out of 827 TACEs, none of them fatal. Embolization seems to play a major role in causing complications during chemotherapy. Biliomas secondary to injection of iodized oil and focal bile duct strictures by gelatine sponge particles have been described [11].

The frequency of bile duct necrosis is probably underestimated because liver biopsy is rarely performed following TACE. A postmortem study by Kobayashi et al. [18] described bile duct injury after TACE in 9% of patients treated for hepatocellular carcinoma. These abnormalities were restricted to large intrahepatic or septal bile ducts. The inner layer vessels of the peribiliary plexus were also reduced. These complications were not detected before patients’ deaths.

Sakamoto et al. [19] tried to identify predisposing factors of bilioma after TACE, a complication that occurred in 3.6% of the patients in their study. The incidence was higher under the following conditions: non hepatocellular tumors (the absence of liver fibrosis reduces uptake of the chemotherapeutic agent), main tumor more than 5 cm in diameter (causing greater diffusion in the normal liver), intrahepatic bile duct enlargement and anti-cancer drug used during the procedure. Segmental or subsegmental TACE tended to induce bile duct injury more often than proximal TACE. The amount of iodized oil gelatine sponges injected as well as the total number of TACE do not seem to influence the development of bile duct necrosis [19, 20]. It is interesting to note that none of the patients in these studies had endocrine tumors.

Imaging (CT scan and magnetic resonance imaging) may help to diagnose bile duct injuries or portal vein obliteration by showing bile duct dilatation, collection, narrowing or obliteration of the portal vein. The delay between TACE and the development of atrophic hepatic segments at CT varies from 2 to 5 months [21, 22]. Yu et al. [21] have estimated that hepatic atrophy related to ischemic injury was especially favored by decreased portal venous perfusion.
Bile ducts are fed exclusively by the hepatic artery and do not have a dual blood supply. Embolization induces peripheral bile duct necrosis as well as ischemic injuries of the nontumoral hepatic parenchyma. In our patient, embolization of all three hepatic arteries during the same procedure might explain the severe ischemia [19, 23]. However, the delayed development of jaundice (three months) after the second TACE was unusual.

**Fig. 1.** CT scan after medium contrast injection (arterial phase) before the first TACE showing multiple liver metastases (white arrows).

**Fig. 2.** CT scan three months after the first TACE. Notice the intense uptake of lipiodol ultrafluid contrast by metastases (white arrows).
**Fig. 3.** a Liver biopsy specimen (coloration with the trichome of Masson) showing cholestasis, extensive fibrosis and biliary duct rarefaction. b High magnification of a.

![Liver biopsy specimen](image1)

**Fig. 4.** Hepatic enzyme variations (xN).

![Hepatic enzyme variations](image2)
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