Ischemic Bile Duct Injury as a Serious Complication After Transarterial Chemoembolization in Patients with Hepatocellular Carcinoma


Abstract
Background: Bile duct injuries after transarterial chemoembolization (TACE) have been reported; however, the exact pathogenic mechanisms and clinical implications of the injuries remain to be clarified. Study: A total of 950 consecutive patients with hepatocellular carcinoma (HCC) were studied. Among them, 807 were treated with TACE and the remaining 143 were treated with transarterial chemoinfusion (TACI) of cisplatin. Results: None of 143 patients with HCC treated with TACI were found to have any radiographic evidence of biliary injury. In contrast, of the 807 patients treated with TACE, 17 (2%) developed biliary complications. Of all complications, 12 (71%) were subcapsular bilomas; 3 (17%), focal strictures of the common hepatic duct or common bile duct; and 2 (12%), diffuse mild dilatation of the intrahepatic bile ducts. Interestingly, 2 of the 12 bilomas were found in the lobe that was not embolized with gelatin sponge particles. The median number of TACE tended to be greater in the patients with focal stricture than in those with bilomas (6.0 vs. 2.5; \( p = 0.08 \)). All 3 patients with focal strictures and 4 of the 12 patients with bilomas had associated serious bacterial infections at presentation. Conclusions: Bilomas seem to be caused by iodized oil rather than gelatin sponge particles; focal strictures of large bile ducts seem to be caused by gelatin sponge particles. We suggest that adjustments in the amounts of iodized oil or gelatin sponge particles and in the sites of embolization may reduce ischemic biliary injuries after TACE.

Key Words: Ischemic bile duct injury—Transarterial chemoembolization—Hepatocellular carcinoma.

Transarterial chemoembolization (TACE), which involves the infusion of iodized oil mixed with chemotherapeutic agent followed by the administration of gelatin sponge particles, has been widely used as an effective palliative treatment modality for patients with unresectable hepatocellular carcinomas (HCCs). However, complications, such as gastric ulcer and cholecystitis, have occurred after this procedure. These complications are usually caused by the overflow of embolic particles from the proper hepatic artery to the gastroduodenal artery or cystic artery. Although bile duct injuries also have been reported, the exact incidence, pathogenesis, and clinical significance remain to be clarified. In this study, we evaluated the frequencies, patterns, and clinical implications of ischemic bile duct injuries after TACE in patients with HCC. We also attempted to determine the predisposing factors and possible pathogenic mechanisms and suggest measures to prevent these serious complications.

MATERIALS AND METHODS

We retrospectively analyzed the medical records and radiologic findings of 950 consecutive patients with HCC who had been treated with TACE or transarterial chemoinfusion (TACI); of those, 807 patients were treated with TACE. After angiographic access was obtained, about 10 mL of iodized oil (lipiodol; Guerbet, Aulnay-sous-Bios, France) mixed with cisplatin was injected via catheter, the tip of which was advanced into the proper hepatic artery. This was followed by selective embolization of the feeding artery with gelatin sponge particles (Gelfoam; Upjohn, Kalama-zoo, MI, U.S.A.). The doses of lipiodol were adjusted depending on the sizes of the tumors.

Gelfoam pieces with nonionic contrast medium were injected via catheter until the hepatic arterial branches were occluded. We used a 5F 75-cm Rosch hepatic catheter and a microferret-18-infusion catheter (Cook, Bloomington, IN, U.S.A.). The remaining 143 patients with main portal vein thrombosis were treated with TACI, which consists of the infusion of cisplatin alone without embolization. Serum biochemistry, \( \alpha \)-fetoprotein levels, and computed tomographic scans were examined serially before and 4 weeks after every treatment. Transarterial chemoembolization was repeated every 12 weeks, and TACI was repeated at 4-week intervals.

RESULTS

Ischemic Biliary Complications After Transarterial Chemoembolization

None of 143 patients with HCC treated with TACI developed any ischemic biliary injury. In contrast, of the 807
patients treated with TACE, 17 (2.1%) developed biliary complications with no evidence of direct invasion of HCC. Baseline characteristics and changes of the bile ducts in the patients with HCC who had biliary complications are presented in Table 1. Of the 17 patients, 14 were male and the mean age was 57 years. Most of the patients were positive for serum hepatitis B surface antigen (88%). All except for two of the patients had relatively good hepatic reserve functions with Child–Pugh score A, and the portal veins were also patent in all except for four who had thrombus in the right portal vein. There were only three patients with small HCCs, defined as being less than 3 cm in longest diameter. Nine patients had single-nodular HCCs; the remaining patients had multinodular HCCs.

Of the 17 patients with biliary complications, 12 (71%) had subcapsular bilomas that averaged 6.8 cm in size (Fig. 1), 3 (18%) had focal strictures of the common hepatic duct (CHD) (Fig. 2) or common bile duct with marked secondary dilatation of the intrahepatic bile duct (IHD), and 2 (11%) had mild diffuse dilatations of the IHD. The diffuse IHD dilatations were found incidentally on follow-up computed tomographic scans and required no treatment. All 3 patients with focal strictures and 4 (33%) of the 12 patients with bilomas had associated bacterial infections at presentation, which required urgent drainage procedures to control them (Fig. 1). Moreover, two patients with focal strictures of the large bile ducts required surgical management despite a drainage procedure. In one of the three patients with focal stricture, a right lobectomy with hepaticojejunostomy was necessary because of a focal stricture of the CHD that was complicated by cholangitis. The tissue showed a thick fibrous band at the stricture site of the CHD; also, epithelial cells of the bile duct were denuded and the stricture site was associated with extensive periductal fibrosis, with no evidence of malignancy (Fig. 3).

Interestingly, 2 (17%) of the 12 bilomas were found in the lobe that was not embolized with Gelfoam. In the patients whose common hepatic arteriogram after segmental embolization of the right hepatic artery showed intact left hepatic artery, computed tomographic scans obtained 4 weeks after the session of TACE revealed saccular cystic lesions, suggesting bilomas in the left lobe of the liver, which was not embolized with Gelfoam. The median numbers of TACE tended to be greater in the patients with focal stricture than in those with bilomas (6.0 vs. 2.5; p = 0.08).

**DISCUSSION**

We observed various patterns of bile duct changes after TACE, which we categorized as three types: biloma, focal stricture of large bile ducts, and diffuse dilatation of IHD. Bilomas were the most common type of biliary complications after TACE in our series; however, the incidence of mild diffuse dilatation of IHD could be underestimated as they were usually asymptomatic and may not have been detected by computed tomographic scans.

Seven (41%) of the 17 patients with biliary complications had associated serious bacterial infections at presentation; in particular, all three cases with focal stricture presented with biliary infections with progressive jaundice. In contrast, 4 of the 12 patients with biloma and none of those with diffuse dilatations of IHD experienced biliary infection during follow-up. Moreover, two patients with fo-

**TABLE 1. Clinical characteristics of patients with HCC with ischemic biliary complications after TACE**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (y)/sex</th>
<th>Etiology</th>
<th>Child class</th>
<th>Tumor type</th>
<th>Location of tumor</th>
<th>Size (cm)</th>
<th>PVT Type</th>
<th>Location</th>
<th>Biliary injury</th>
<th>TACE No.</th>
<th>Associated with</th>
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<tbody>
<tr>
<td>1</td>
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<td>NBNC</td>
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<td>SN</td>
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<td>CHD</td>
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<td>HBV</td>
<td>A</td>
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<td>HBV</td>
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<td>HBV</td>
<td>A</td>
<td>MN</td>
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<td>BL</td>
<td>Right IHD</td>
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<tr>
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<td>49/M</td>
<td>HBV</td>
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<td>Left IHD</td>
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<td>52/F</td>
<td>HCV</td>
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<td>Left IHD</td>
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<td>Left IHD</td>
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PVT indicates portal vein thrombosis; NBNC, non-B and non-C; HBV, hepatitis B virus; HCV, hepatitis C virus; SN, single nodular; MN, multinodular; CBD, common bile duct; FS, focal stricture; BL, biloma; DD, diffuse dilatation; M, male; F, female; +, yes; −, no.
cal strictures of the large bile ducts required surgical management despite a drainage procedure. These data suggest that focal strictures of large bile ducts after ischemic injuries are more likely to be associated with serious biliary infections than other patterns of biliary changes located in the peripheral bile ducts.

Several possible mechanisms can be involved in the cause of such ischemic injuries of the bile ducts after TACE. Theoretically, Gelfoam, lipiodol, cisplatin, or mechanical vascular injuries during the procedure could induce the injuries. There have been some reports of sclerosing cholangitis after treatment with hepatic arterial floxuridine chemotherapy.\textsuperscript{13–15} In these studies, it had been suggested

**FIG. 1.** A 62-year-old female patient with HCC with infected biloma after TACE. **A:** Computed tomographic scan obtained after the 5th session of TACE for HCC in the left lobe of liver shows a 7 × 5-cm cystic lesion (arrow) in the left lateral segment of the liver associated with dilatation of adjacent bile ducts. Note the tumor treated with lipiodol (arrowhead) in the same lobe. **B:** In this patient, drainage of the biloma was needed because of secondary bacterial infection. The biloma cavity communicated with the bile ducts (arrow).

**FIG. 2.** A 57-year-old male patient with HCC with a focal stricture of CHD after TACE. Cholangiogram shows a smooth-surfaced focal stricture of the proximal CHD (arrow), suggesting a benign stricture.

**FIG. 3.** Histologic features in a patient with HCC with an ischemic stricture of CHD after TACE. **A:** A 10- × 9- × 7-cm mass associated with adjacent diffuse necrosis and diffusely fibrotic CHD wall (arrow). **B:** Bile duct epithelia were totally denuded (arrow) and the periductal area was replaced by extensive fibrosis (arrowhead) because of ischemic injuries after TACE (hematoxylin and eosin stain; original magnification, ×100).
that hepatic arterial infusion of chemotherapeutic agents, such as hepatic arterial fluorouridine, might result in hepatic arterial fibrosis; however, in our study, none of the 143 patients with HCC treated with TACE presented with ischemic biliary injury. This finding suggests that cisplatin may have no effect on the development of biliary injury after TACE, although it has been reported to produce vascular injuries when injected intravenously.16

Biloma is an encapsulated collection of bile, which has been sealed off by the adhesive epithelialization process,17–19 that has been reported after cholecystectomy, resulting from direct injury to the biliary tree.20 Hepatic arterial branches primarily supply the biliary tree, which gives off a vascular plexus around the bile ducts (peribiliary plexus).21,22 Biloma induced after TACE seems to be a consequence of occlusion of small peripheral hepatic arteries with lipiodol, followed by bile duct epithelial necrosis. In a postmortem study of patients with HCC treated with TACE, about one half of the nonnecrotic bile ducts adjacent to the necrotic bile ducts of bilomas demonstrated marked reduction of the inner layer of vessels.23 Lipiodol has been known to occlude such small peripheral vessels,24,25 especially at the level of peribiliary capillary plexus. Interestingly, in our study, 2 (17%) of 12 bilomas were found at the lobe that was not embolized with Gelfoam. This finding suggests that biloma may be caused by lipiodol rather than Gelfoam as lipiodol was injected via the proper hepatic artery and Gelfoam embolization was done selectively in the lobar branch of the hepatic artery. Ischemic injury to such peripheral intrahepatic ducts seems to cause the leak of bile and formation of bile cysts. Subsequently, as granulation tissues grow into the area, the formation of surrounding fibrous tissue limits the extent of the biloma.26 Lipiodol is cleared from normal liver parenchyma within 7 days,27,28 thus, such injury seems to occur before a week.

In contrast, focal strictures of large bile ducts seem to be the result of repeated ischemia for prolonged periods by embolization with Gelfoam. The extrahepatic bile ducts are supplied with blood from various sources; the CHD receives blood supply from right and left hepatic artery; the common bile duct receives blood mainly from retroduodenal and gastroduodenal arteries.29 Gelfoam can obliterate the larger and more proximal feeding arteries of tumors, whereas smaller particles of lipiodol embolize only peripheral arterial branches.24,30 In this study, we have demonstrated that the pathologic features of a narrowed bile duct after repeated TACE using Gelfoam were intense fibrosis and granulation tissue associated with denudation of epithelial layer; however, there were relatively few signs of inflammation in the tissues of bile ducts. Thus, we speculated that repeated embolization with Gelfoam resulted in ischemic arteritis, followed by the chronic inflammation of large bile ducts, which eventually lead to focal extensive fibrosis.

The number of TACE was greater in patients with focal stricture than in those with biloma. This finding suggests that repeated direct mechanical injuries to vessel walls caused by the catheter might play some role in the pathogenesis of focal strictures of the large bile duct. In our cases, focal strictures were located at the CHD level or in large bile ducts adjacent to the CHD level, with none in the distal common bile duct. The poor collateral supply to the CHD compared with the abundant collaterals to the lower common bile duct could explain the vulnerability of CHD to the ischemic injuries caused by the occlusion of feeding arteries.31–33

When patients with HCC treated with TACE manifest progressive obstructive jaundice while the tumors are stable or in remission, one should suspect ischemic bile duct injuries, especially focal stricture of large ducts, as a complication of the procedure.13 To prevent this type of biliary injury, the catheter should be inserted more selectively into the peripheral arteries, if possible, when using Gelfoam as an embolic substance. It is also necessary to perform the procedure carefully, considering the amount and the size of Gelfoam particles and the individual characteristics of vascular anatomy.9

In conclusion, ischemic bile duct injuries were not uncommon in patients with HCC treated with TACE. Biloma seems to be associated with ischemic injuries of small bile ducts that are probably caused by lipiodol rather than Gelfoam, which is in contrast to focal strictures of large bile ducts after repeated ischemia for prolonged periods by embolization with Gelfoam. We suggest that most of the focal strictures of large bile ducts and, occasionally, bilomas may be complicated with serious biliary infections, which necessitate urgent biliary drainage procedures. We also suggest that adjustments in the amounts of lipiodol or Gelfoam and in the sites of embolization may reduce the risk of ischemic biliary injuries after TACE in patients with HCC.

REFERENCES