Extrahepatic biliary obstruction after percutaneous tumour ablation for hepatocellular carcinoma: aetiology and successful treatment with endoscopic papillary balloon dilatation

N Sasahira, M Tada, H Yoshida, R Tateishi, S Shiina, K Hirano, H Isayama, N Toda, Y Komatsu, T Kawabe, M Omata

Background and aims: Percutaneous tumour ablation (PTA), such as ethanol injection and radiofrequency ablation, is now recognised as a primary treatment for hepatocellular carcinoma (HCC). Although PTA is a relatively safe procedure, it can cause biliary obstruction as a rare complication. As patients with cirrhosis undergoing surgery or endoscopic retrograde cholangiopancreatography/sphincterotomy have a high mortality rate from bleeding, we adopted the use of endoscopic papillary balloon dilatation (EPBD) in these patients and now report the results. We retrospectively analysed the incidence of biliary obstruction after PTA and the efficacy of treatment with EPBD.

Patients and methods: A total of 1043 patients with HCC were treated by PTA, of whom 538 were treated with transcatheter embolisation with up to eight years of follow up.

Results: There were 17 (1.6%) cases of hilar obstruction due to tumour progression and 35 (3.4%) cases of extrahepatic obstruction. Apart from the expected causes of biliary obstruction (haemobilia n = 11, gallstones n = 11, and three miscellaneous causes), we found that 10 patients had obstruction due to biliary casts. This is the first description of biliary casts after percutaneous tumour ablation therapy. Extrahepatic biliary obstruction by procedure related haemobilia occurred within three days of PTA while other causes occurred between 0 and 17 (average 4.9) months. Biliary casts occurred more frequently after ethanol injection than after radiofrequency ablation. EPBD successfully dissipated biliary obstruction in 33 of 35 cases, while two died due to hepatic failure despite successful drainage.

Conclusions: Extrahepatic biliary obstruction is an uncommon complication after PTA for HCC, and can be safely and effectively treated with EPBD, despite impaired liver function.

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide, usually occurring in patients with cirrhosis due to chronic viral hepatitis.1–3. In spite of advances in safety, surgical resection of HCC is still frequently contraindicated because of poor liver function.4 Percutaneous tumour ablation (PTA), such as percutaneous ethanol injection therapy (PEIT) and radiofrequency ablation (RFA), is frequently performed as a primary treatment for HCC.5–7 PTA is applicable even for those with impaired liver function and its safety in general has been well documented. However, several complications are well recognised.8–10 Haemorrhage is the most frequent complication of PTA and is usually treated conservatively.11–13 However, it can lead to biliary obstruction and deterioration in liver function and death. Biliary damage, including haemobilia, is reported to occur in up to 1% of cases treated with PTA.14–16 However, most of these reports covered short term complications during the periprocedural period. There were no reports of obstructive jaundice in a large series of patients after PTA for HCC.

Biliary obstruction is known to occur in patients with HCC due to tumour infiltration or compression of the bile duct, biliary tumour thrombi, spontaneous HCC haemorrhage, and cholecdocholithiasis.17–20 However, endoscopic facilitation of biliary drainage may be life saving in patients with acute suppurative cholangitis and biliary obstruction.21–24 However, patients with HCC have an increased risk of bleeding due to liver dysfunction, and a mortality of up to 50% for surgery and up to 22% for endoscopic sphincterotomy (EST) has been reported for patients with cirrhosis and coagulopathy.25–27 A potentially safer alternative to EST is endoscopic papillary balloon dilatation (EPBD) in which complications such as severe bleeding are rare, even in patients with advanced cirrhosis.28–31 Thus we adopted EPBD as the first line treatment for extrahepatic biliary obstruction occurring in patients with HCC. In this article, we describe our results.

When treating patients with HCC and biliary obstruction who had undergone PTA, we began to recognise that biliary obstruction was frequently caused by biliary casts that were morphologically and histologically distinguishable from haemobilia, tumour thrombi, and common bile duct stones, and were similar to those reported as a complication of liver transplantation.32–34 This paper is the first description of biliary casts that occurred in the course of HCC treated by PTA.

Abbreviations: PTA, percutaneous tumour ablation; HCC, hepatocellular carcinoma; EPBD, endoscopic papillary balloon dilatation; PEIT, percutaneous ethanol injection therapy; RFA, radiofrequency ablation; EST, endoscopic sphincterotomy; US, ultrasonography; CT, computed tomography; TAE, transcatheter embolisation; ERC, endoscopic retrograde cholangiography; ERCP, endoscopic retrograde cholangiopancreatography; γ-GTP, gamma-glutamyl transpeptidase
MATERIALS AND METHODS

Patients

A total of 1043 consecutive patients with HCC were admitted to Tokyo University Hospital from January 1995 to December 2002. They received 8807 sessions of PTA therapy (6322 PEIT, 467 percutaneous microwave coagulation therapy, and 2018 RFA). These 1043 patients consisted of 312 women and 731 men, with a mean age of 66.4 years (range 36–90 years). Eighty five per cent of the patients had cirrhosis, with a Child-Pugh classification of A in 67%, B in 31%, and C in 2% (table 1). The aetiology of liver disease was hepatitis B, hepatitis C, alcohol, and other causes in 11%, 82%, 3%, and 4%, respectively. The diagnosis of HCC was confirmed by percutaneous needle biopsy and histology in 898 of 1043 (86%) patients. The remaining 145 patients were diagnosed on the basis of α-fetoprotein levels. Also, 538 patients (52%) were assessed radiologically and patients were classified as having HCC based on abdominal ultrasonography (US), computed tomography (CT), magnetic resonance imaging, and/or hepatic arterial angiography, together with measurement of α-fetoprotein levels. Also, 538 patients (52%) were treated by transarterial embolisation (TAE) in addition to PTA. All patients treated with PTA were followed up until recurrence or another occurrence of HCC, with monthly clinical examinations and blood tests, and every three months by abdominal US and/or CT scan, primarily to survey recurrence or another occurrence of HCC, with monthly PTA. All patients treated with PTA were followed up until recurrence of HCC. The cause of biliary obstruction in all of these cases was either direct invasion of HCC or tumour thrombi into the bile duct.11–13

RESULTS

Hilar bile duct obstruction

Forty seven of 1043 (4.5%) patients with HCC treated with PTA over eight years presented a total of 52 episodes of obstructive jaundice (table 1). There were 17 cases of hilar bile duct obstruction. Five of these 17 patients had a history of successful treatment of extrahepatic biliary obstruction. Hilar or intrahepatic obstruction of the bile duct were primarily treated by percutaneous transhepatic biliary drainage as many had multiple intrahepatic bile duct occlusions. The cause of biliary obstruction in all of these cases was either direct invasion of HCC or tumour thrombi into the bile duct.11–13

Extrahepatic bile duct obstruction

Cases of extrahepatic bile duct obstruction

There were 35 cases of extrahepatic bile duct obstruction (table 1). Extrahepatic biliary obstruction was due to choledocholithiasis in 11 cases, biliary casts in 10, haemobilia in 11, and miscellaneous causes in three (table 2). One of the novel observations of this study was the finding of casts in the biliary tree. Casts were composed of sludge that had become confluent and had assumed a shape conforming to the biliary tree. Typical choledochographic and endoscopic appearances of the casts in our series are shown in fig 1. Analysis of the casts performed for three of the 10 patients showed that they mainly consisted of acellular biliary material with or without bacterial colonies, fragments of bile duct epithelium, or collagen tissue. These findings were similar to those observed in previous reports of casts from patients after liver transplantation.28–30 Haemobilia was characterised as vague irregular margins by cholangiography, and was frequently distributed within multiple intrahepatic bile ducts.31 The remaining three cases of biliary obstruction...
were due to chronic pancreatitis, bile duct stenosis secondary to local ethanol injection, and one case was undetermined. The clinical backgrounds of the patients were similar, regardless of the cause of biliary obstruction, and there were no differences in terms of age, sex, Child-Pugh score, prothrombin time, or platelet count (data not shown). It was noted that biliary casts and haemobilia occurred more frequently in men (that is, nine males and one female for casts, and 10 males and one female for haemobilia), although this was not statistically significant (p = 0.3 and 0.19, respectively; Fisher’s exact test).

**Characteristics of clinical parameters**

The average time from the last PTA to the development of biliary obstruction was approximately six months for patients with stones and about three months for patients with casts. Haemobilia generally occurred immediately after percutaneous tumour ablation (eight of 11 patients). It was probably due to procedure related bleeding, such as puncture of vessels in or around the HCC with the bile duct. However, haemobilia was also observed 2–10 months (average: 5.3 months) after percutaneous tumour ablation and was probably due to spontaneous bleeding from a HCC (table 2).

The concentration of serum bilirubin was noticeably higher in patients with haemobilia than in those with casts and haemobilia occurred more frequently in men (that is, nine males and one female for casts, and 10 males and one female for haemobilia), although this was not statistically significant (p = 0.3 and 0.19, respectively; Fisher’s exact test).

**Efficacy of endoscopic treatment**

Thirty three of the 35 cases with extrahepatic bile duct obstruction were treated by endoscopic balloon dilatation. The clinical backgrounds are outlined in table 2. No patient received blood products before EPBD and prophylactic antibiotics were used routinely prior to EPBD.

EPBD was successfully performed in all 33 cases, regardless of liver cirrhosis and including those with an advanced condition. After EPBD, stones, biliary casts, or haemobilia in the bile duct were removed using such devices as a basket catheter (FG-22Q; Olympus Optical Co., Tokyo, Japan) and a retrieval balloon catheter (Zeon Medical Inc., Tokyo, Japan). Temporary plastic stents and nasobiliary drainage tubes were used in five (four cases, stents; one case, drainage tube) of 11 cases with choledocholithiasis, in two (one and one) of 10 cases with biliary casts, and in seven (0 and seven) of 11 cases with choledocholithiasis, in two (one and one) of 10 cases with biliary casts, and in seven (0 and seven) of 11 cases with haemobilia, respectively, and left for approximately one week. In two cases with haemobilia, nasobiliary drainage was continued for up to one month. In one biliary cast case, two plastic stents (one in the common bile duct and the other in the gallbladder) were placed for two years, exchanging them every three months, because of the presence of fistulas between the liver abscess, gallbladder, and lung, and also because of biliary stricture in the common bile duct. These complicated fistulas were relieved by stenting, and there was no recurrence after their removal. All cases with biliary stones and casts were treated successfully without complications, except for one with bleeding that required blood transfusion and additional interventional therapy for haemostasis, including TAE of the branches of the posterior superior pancreaticoduodenal artery. This patient did not have severe thrombocytopenia or coagulopathy (platelet count 8.3×10^3/μl, prothrombin time 72.8%). The common bile duct stone in this patient was a maximum of 20 mm in diameter and had a sharp margin that damaged the papilla during extraction. There were no other bleeding complications in the remaining patients treated with EPBD. Serious complications, such as perforation or severe pancreatitis, did not occur. The only other complication was a case with mild pancreatitis according to Cotton’s criteria. Of eight patients with haemobilia related to PTA, three suffered from persistent haemorrhaging into the bile duct after extracting coagulated blood into the duodenum by

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**Table 2** Cholangiographic and clinical variables among different categories of extrahepatic bile duct obstruction

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cast (n = 10)</th>
<th>Stones (n = 11)</th>
<th>Haemobilia (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period after initial PTA (months)</td>
<td>7–72 (32)</td>
<td>0–88 (27)</td>
<td>0–42 (7.8)</td>
</tr>
<tr>
<td>Period after latest PTA (months)</td>
<td>0–12 (5)</td>
<td>0–17 (6.5)</td>
<td>30–99 (55)</td>
</tr>
<tr>
<td>T bilirubin (mg/dl)</td>
<td>0.5–4.1 (2.0)</td>
<td>1.0–15.9 (4.3)</td>
<td>1.7–26.3 (7.9)</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU/l)</td>
<td>146–1485 (553)</td>
<td>248–1065 (417)</td>
<td>229–787 (470)</td>
</tr>
<tr>
<td>γ-GTP (IU/l)</td>
<td>51–952 (268)</td>
<td>34–253 (110)</td>
<td>53–649 (267)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4/10 (40%)</td>
<td>6/11 (55%)</td>
<td>4/8 (50%)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>0/10 (0%)</td>
<td>3/11 (27%)</td>
<td>0/8 (0%)</td>
</tr>
<tr>
<td>Liver abscess</td>
<td>5/10 (50%)</td>
<td>2/11 (18%)</td>
<td>0/8 (0%)</td>
</tr>
<tr>
<td>Gallstone</td>
<td>2/20 (10%)</td>
<td>10/10 (100%)</td>
<td>0/8 (0%)</td>
</tr>
<tr>
<td>“Haemobilia sign”</td>
<td>1/10 (10%)</td>
<td>0/11 (0%)</td>
<td>8/10 (80%)</td>
</tr>
<tr>
<td>Biliary strictures</td>
<td>9/10 (90%)</td>
<td>2/11 (18%)</td>
<td>1/8 (13%)</td>
</tr>
<tr>
<td>Type of PTA (PEIT/PMCT/RFA)</td>
<td>10/2/1</td>
<td>9/1/2</td>
<td>8/0/0</td>
</tr>
<tr>
<td>History of TAE</td>
<td>8/10 (80%)</td>
<td>6/11 (55%)</td>
<td>2/8 (25%)</td>
</tr>
<tr>
<td>Size of HCC (cm)</td>
<td>0–8.5 (2.9)</td>
<td>0–7.5 (3.2)</td>
<td>1.5–6 (3.4)</td>
</tr>
<tr>
<td>PVTT</td>
<td>1/10 (10%)</td>
<td>1/11 (9%)</td>
<td>2/8 (25%)</td>
</tr>
<tr>
<td>Additional therapy</td>
<td>None</td>
<td>None</td>
<td>TAE 1</td>
</tr>
<tr>
<td>Immediate prognosis</td>
<td>Recovered</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>Recovered</td>
<td>10/10 (100%)</td>
<td>11/11 (100%)</td>
<td>6/8 (75%)</td>
</tr>
<tr>
<td>Died</td>
<td></td>
<td></td>
<td>2/8 (25%)</td>
</tr>
</tbody>
</table>

PTA, percutaneous tumour ablation; HCC, hepatocellular carcinoma; T bilirubin, total bilirubin; PEIT, percutaneous ethanol injection therapy; PMCT, percutaneous microwave coagulation therapy; RFA, radiofrequency ablation; TAE, transarterial embolisation; PVTT, portal vein tumour thrombus; γ-GTP, gamma-glutamyl transpeptidase.
basket catheter and balloon retrieval. TAE was successfully performed in one of these cases, but liver function was too poor to perform TAE in the remaining two and they died of hepatic failure 25 and 40 days after EPBD. Autopsies of these two cases suggested that the invading HCC itself had caused the haemorrhage spontaneously.

**DISCUSSION**

Obstructive jaundice in HCC patients is usually due to extrahepatic obstruction or hilar bile duct obstruction. Hilar bile duct obstruction is a relatively rare but well known complication of HCC, usually caused by direct infiltration or compression by the tumour. There were 17 (1.6%) cases of hilar obstruction among our 1043 patients, an incidence comparable with the previously reported 2–3%. In addition, we found 35 (3.4%) cases of extrahepatic biliary obstruction, most of which were not caused by direct invasion of the HCC. Causes were divided almost equally into three categories: biliary cast, cholelithiasis, and haemobilia.

Biliary casts were composed of sludge that had become confluent and assumed a shape conforming to the biliary tree. Although pathological confirmation was available in only three of the 10 cases, we assumed that the remaining seven cases had casts based on their typical cholangiographic and endoscopic appearance. Biliary cast formation had been previously reported mainly as a sequel of liver transplantation, occurring up to several months after the procedure. A similar interval between PTA and the development of biliary cast obstruction was observed in this study. A connection was suggested between ischaemia and cast formation after liver transplantation. Ischaemia of the bile duct was also reported in patients with HCC after TAE, and the majority of patients showing biliary casts had a history of TAE prior to PTA. Therefore, TAE appears to be a cause of bile cast formation. However, although TAE has been a commonly used procedure, there have been no reports on biliary cast formation in these patients. This suggests that PTA itself may have played a role in bile cast formation. One possibility is that the ablation material, ethanol, may have leaked into the bile duct and triggered cast formation, possibly by damaging the bile duct epithelium. Indeed, most of the patients with bile casts had undergone PEIT as the modality of PTA (table 2).

Biliary obstruction due to haemobilia occurred either immediately after percutaneous tumour ablation or after a long interval. Immediate haemobilia is the most common—it is associated with percutaneous tumour ablation. Great care is taken not to penetrate the portal vein with the ablation needle, and haemorrhage became less with increased clinical experience. On the other hand, haemobilia occasionally occurs late after percutaneous tumour ablation, is secondary to tumour growth, and carries a poor prognosis. It was not related to the procedure but rather to the growth of HCC, presenting a poor prognosis.

Gallstone formation is a common complication in cirrhosis, and biliary obstruction due to gallstones is unlikely to be related to PTA. Nevertheless, subsequent obstructive supplicative cholangitis, sometimes associated with pancreatitis, is an extremely serious problem, especially in cirrhotic patients, and a high mortality has been reported after treatment by surgery as well as after EST. However, we were able to successfully remove the common bile duct stones in all of our patients.

Tumour fragments or tumour casts have been reported to cause biliary obstruction in HCC patients but there was no such case in the present series. Tumour casts are reported to be soft, grayish-white, and resemble chicken fat, in contrast with the amorphous, dark brownish, or black coloured biliary cast.

In the present study, all patients with extrahepatic biliary obstruction treated by EPBD had impaired liver function. Twenty eight patients (85%) were assessed as Child-Pugh grade B or C, with the most prolonged prothrombin activity (34.5%), the lowest platelet count (37 000/μL), and the highest bilirubin concentration (29 mg/dl), all of whom
would have been considered as having a poor prognosis with more invasive treatments. There were no complications, except for one case of ensuing mild pancreatitis and one of moderate bleeding.

In conclusion, the major causes of extrahepatic biliary obstruction after PT are biliary casts, haemobilia, and common bile duct stones. The biliary cast appeared to be a complication specific to PT, and PEIT in particular. All cases were successfully treated with EPBD in spite of impaired liver function.

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Conflict of interest: None declared.

REFERENCES