Received: 11 November 2020 | Revised: 19 December 2020 | Accepted: 6 January 2021

DOI: 10.1002/ccr3.3828

CASE REPORT

Clinical Case Reports Open Access WILEY

Hepatocellular carcinoma recurrence in the extrahepatic bile duct wall: A case report

Taku Matsumoto | **Toshihiko Yoshida** | **Takashi Yamagishi** | **Hironobu Goto** | **Dai Otsubo** | **Akinobu Furutani** | **Hisoka Yamane** | **Yasuhiro Fujino** | **Masahiro Tominaga**

Department of Gastroenterological Surgery, Hyogo Cancer Center, Akashi, Japan

Correspondence
Taku Matsumoto, Department of Gastroenterological Surgery, Hyogo Cancer Center, 13-70, Kitaoji-cho, Akashi, Hyogo 673-8558, Japan.
Email: mattak2006@yahoo.co.jp

Funding
No funding was used to support this study.

Abstract

We should know that hepatocellular carcinoma can progress as if it replaces the bile duct wall itself.

KEYWORDS

bile duct invasion, bile duct wall, hepatocellular carcinoma

1 | BACKGROUND

Bile duct invasion (BDI) is a relatively rare presentation of hepatocellular carcinoma (HCC). Under such conditions, invasion of tumor cells in the bile duct lumen and subsequent growth of a bile duct tumor thrombus (BDTT) is known to be the most common state in BDI. This type of HCC often presents with obstructive jaundice and has been well documented as "icteric type hepatoma" in several reports.[1-3] However, little is known about the morphology of BDI other than these observations because there are very few reports focused on the diversity of BDI. Here, we report an extremely rare case of recurrent HCC with a unique form of BDI, which spread as if the bile duct wall was replaced without a tumor thrombus.

2 | CASE PRESENTATION

A 50-year-old man, who was found to have HCC diagnosed with an increase in tumor marker alpha-fetoprotein (AFP) at a previous hospital, was referred to our hospital for treatment three years prior. At the first visit, no clinical symptoms were observed. Computed tomography (CT) revealed a round tumor 2 cm in diameter at the root of the right hepatic duct in the boundary area between segments 4 and 5 of the liver (Figure 1). We then performed cholecystectomy and tumor enucleation. On postoperative histological examination, the tumor was a moderately differentiated HCC, and a cancer-positive margin was suspected in a part of the resected specimen. This meant that the cancer seemed to be exposed in a part of enucleated tumor by microscopic observation, but we thought it was unclear whether the cancer cells actually remained in the remnant liver or not. Therefore, we decided to follow up on diagnostic imaging tightly, and we were thinking of re-resection immediately if the remnant of HCC appeared. After the surgery, the patient was observed carefully in our outpatient setting. Although the level of tumor marker alpha-fetoprotein (AFP) decreased from 234.4 ng/mL to 50 ng/mL one month after the surgery, it increased gradually thereafter. Finally, the AFP level increased to 322.5 ng/

Abbreviations: AFP, alpha-fetoprotein; BDI, bile duct invasion; BDTT, bile duct tumor thrombus; CT, computed tomography; HCC, hepatocellular carcinoma; PIVKA-II, protein induced by vitamin K absence or antagonist-II.

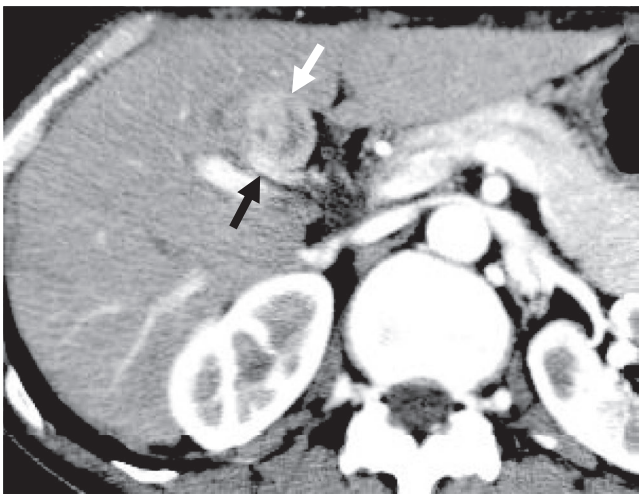

FIGURE 1 CT at the time of the initial surgery. A round tumor (white arrow) approximately 2 cm in diameter was in contact with the root of the right hepatic duct (black arrow). CT, computed tomography

right hepatic duct (Figure 4A). Endoscopic retrograde cholangiopancreatography demonstrated obstruction of the right hepatic duct and extensive irregularities in the extrahepatic bile duct wall (Figure 4B). An endoscopic biopsy of the bile duct wall revealed malignant cells, but a definitive diagnosis could not be made. Contrast-enhanced CT demonstrated enhanced wall thickening of the bile duct from the upper margin of the pancreas to the root of the left hepatic duct (Figure 4C). Ultrasonography also revealed the wall thickening of dilated extrahepatic bile duct, but there was no tumor detected in the liver parenchyma (Figure 4D).

Abnormal laboratory findings immediately before the surgery were as follows: white blood cell count, 2400/μL; red blood cell count, 3,900,000/μL; hemoglobin, 10.4 g/dL; AFP, 322.5 ng/mL; and PIVKA-II, 117 mAU/mL. The serum surface antigen of the hepatitis B virus (0.99 IU/ml) and anti-hepatitis B core antibody levels (9.83 S/CO) were positive. He was thought to be an inactive carrier of hepatitis B. The blood serum hepatobiliary enzymes, including total bilirubin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase, were within normal ranges.

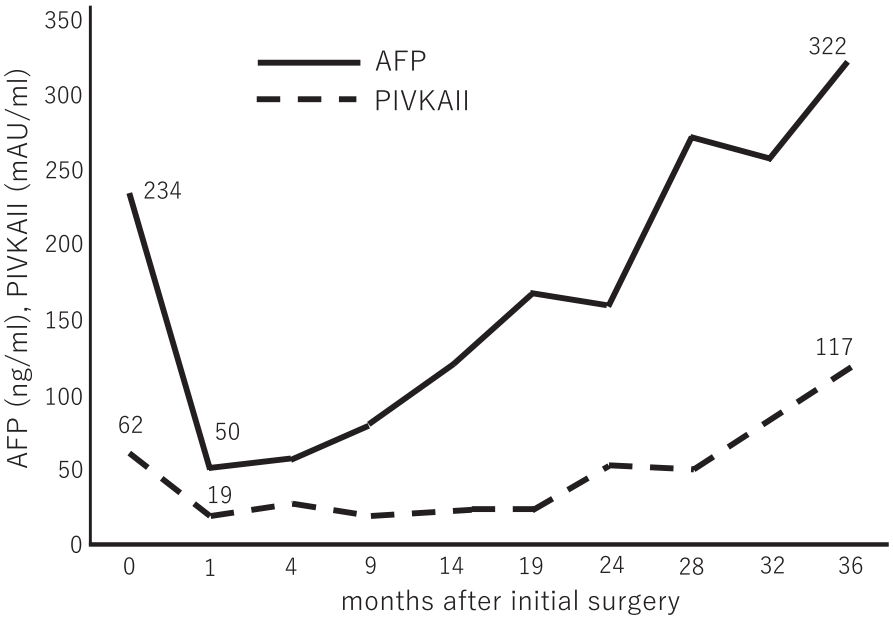

FIGURE 2 Changes in AFP and PIVKA-II levels after the initial surgery. AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II

mL three years after the surgery. Changes in the levels of AFP and protein induced by vitamin K absence or antagonist-II (PIVKA-II) are shown in Figure 2. During this period, we acquired various diagnostic images, but we could not identify any findings of recurrence, and the patient had no clinical signs such as jaundice. Approximately three years after the initial surgery, CT indicated abnormal thickness of the extrahepatic bile duct wall. When we compared the several CT images acquired up to that point, this part of the extrahepatic bile duct wall had gradually been thickening and had become well enhanced (Figure 3). Therefore, we decided to examine this portion of the bile duct in detail.

Magnetic resonance cholangiopancreatography revealed stenosis of the bile duct of the hepatic hilum, especially the

Finally, the patient was diagnosed with recurrent HCC in the extrahepatic bile duct wall. Judging from the images, the tumor was located mainly in the right hepatic duct and extended to the root of the left hepatic duct and common bile duct at the upper margin level of the pancreas. Therefore, right hepatic lobectomy, caudate lobectomy, extrahepatic bile duct resection, and bile duct reconstruction were performed after percutaneous transhepatic portal embolization of the right lobe of the liver because the estimated remnant liver volume was small.

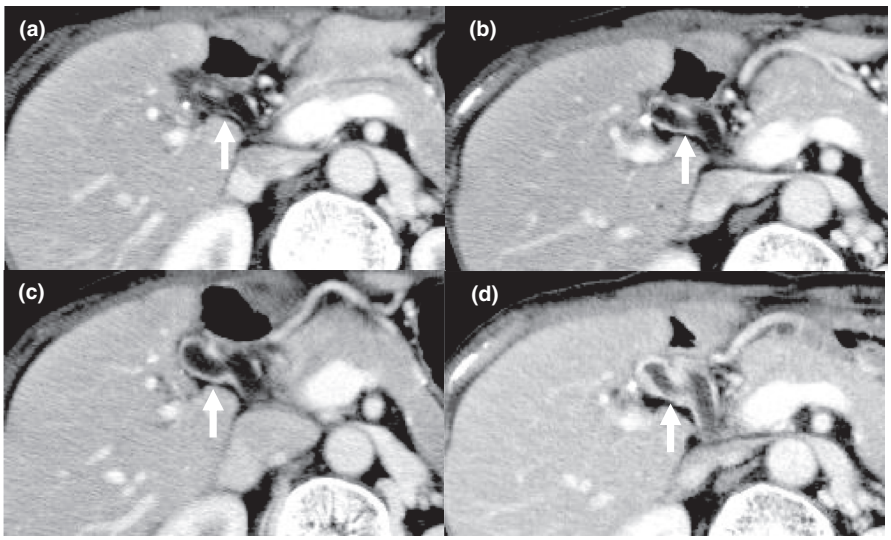

FIGURE 3 Changes in CT findings after the initial surgery. **A**, **B**, **C**, **D** The extrahepatic bile duct wall had been gradually thickening 4 months, 11 months, 24 months, and 36 months after the initial surgery, respectively (arrow). CT, computed tomography

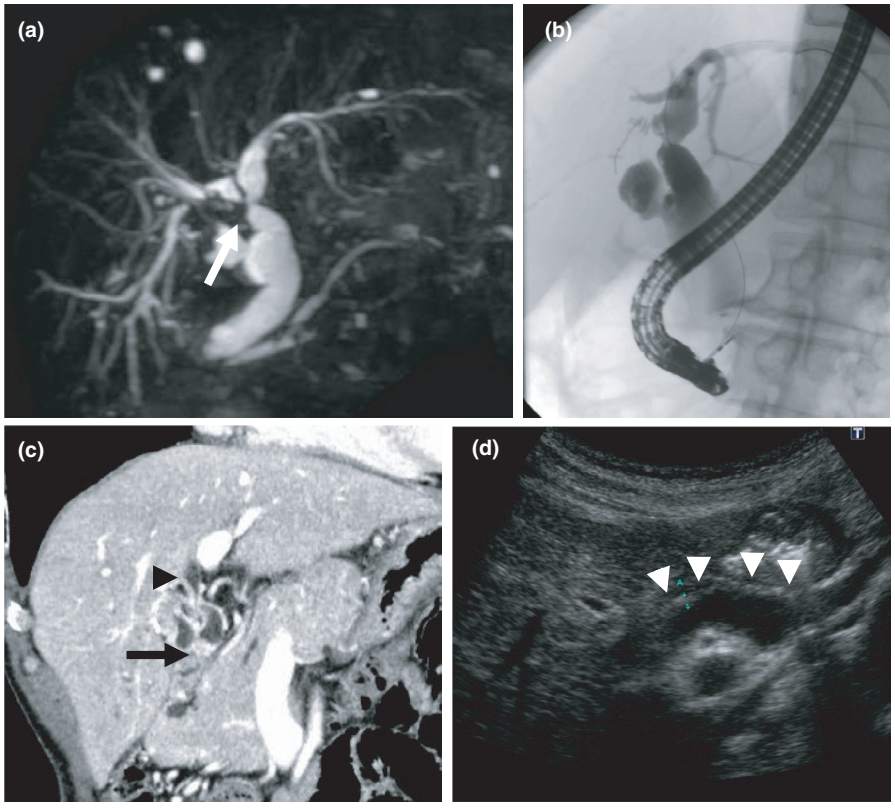

FIGURE 4 Imaging findings of the bile duct before the second surgery. **A,** Magnetic resonance cholangiopancreatography revealed stenosis of the bile duct of the hepatic hilum, especially the right hepatic duct (white arrow). **B,** Endoscopic retrograde cholangiopancreatography demonstrated obstruction of the right hepatic duct and extensive irregularities in the extrahepatic bile duct wall. **C,** Contrast-enhanced CT (coronal view) demonstrated enhanced wall thickening of the extrahepatic bile duct from the upper margin of the pancreas (arrow) to the root of the left hepatic duct (arrowhead). CT, computed tomography. **D,** Ultrasonography revealed the wall thickening of dilated extrahepatic bile duct (white arrowhead)

The resected specimen revealed extensive wall thickening of the extrahepatic bile duct wall (Figure 5). In a section of the right hepatic duct, there was a nodular part involving the bile duct wall. The wall thickening continuously spread from the right hepatic duct to the common bile duct and left hepatic duct (Figure 6A).

Microscopically, in the nodular and thickened part of the bile duct wall, moderately differentiated HCC showing a cord-like structure that had progressed to replace all layers of the bile duct wall (Figure 6B). It was not clear whether the nodular part was a remnant of HCC from the previous surgery. However, there was no other apparent tumor mass or tumor invasion within the liver parenchyma. The resection margins of the distal bile duct and left hepatic duct tested negative for cancer. Immunohistochemical examination demonstrated a positive reaction for hepatocyte paraffin 1 (Figure 6C). Thus, the final diagnosis was recurrent HCC in the extrahepatic bile duct wall.

The postoperative course was uneventful. The levels of both the tumor markers AFP and PIVKA-II decreased

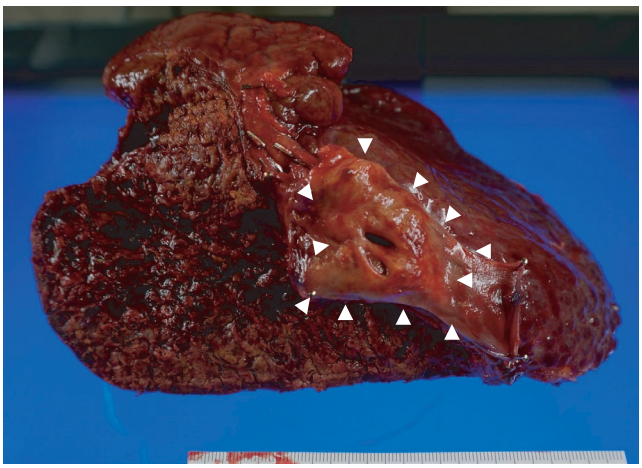

FIGURE 5 Resected specimen in the second surgery. Extensive bile duct wall thickening (arrowhead) was observed around the right hepatic duct

major bile duct.[6,8,9] However, in the present case, the tumor infiltrated the bile duct, replacing all layers of the major bile duct wall without forming a BDTT. We believe this type of BDI is unique and extremely rare as we were unable find any published reports that describe such a progression form.

In the present case, HCC recurred in the extrahepatic bile duct wall after resection of the primary hepatic parenchymal lesion. It is likely that the tumor resected in the initial surgery had already infiltrated the right first-order branch of the bile duct. Afterward, the remnant tumor cells might have spread along the extrahepatic bile duct wall. The mechanisms by which the tumor evolved to replace all layers of the bile duct wall are unclear, but they may have been affected by the procedure of the initial surgery. Despite the gradual wall thickening and enhancement of the bile duct wall as observed on the serial CT images, we could not identify the site of HCC recurrence for approximately three years. We admit that

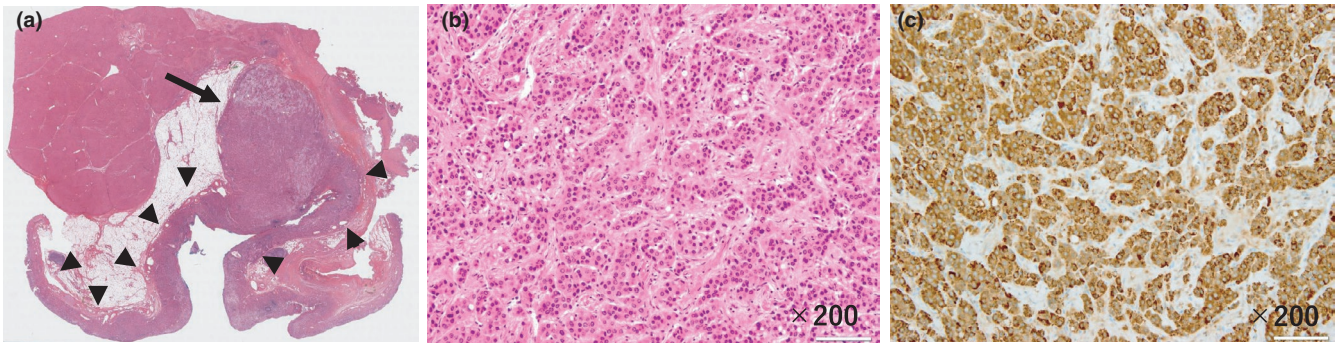

FIGURE 6 Histopathological findings of the resected specimen in the second surgery. **A, B** Roupe and microscopic images after hematoxylin and eosin staining in the section of the right hepatic duct. There was a nodular part (arrow) adjacent to the bile duct wall, and wall thickening had continuously spread to the extrahepatic bile duct (arrowhead). In the thickened part of the bile duct, moderately differentiated HCC showing a cord-like structure progressed to replace all layers of the bile duct wall. **C,** Immunohistochemical staining for hepatocyte paraffin 1. Many positive cells were observed. HCC, hepatocellular carcinoma

immediately to within the normal range. His condition has been favorable without recurrence for 20 months after the second surgery.

3 | DISCUSSION

It is well known that HCC can easily invade the adjacent vascular system, especially the portal vein. However, invasion of the biliary system is relatively rare. According to previous reports, the incidence of BDI is 0.53%-9.2% in patients with HCC.[4-6] In 1947, Mallory et al[7] first reported a patient with HCC presenting with obstructive jaundice caused by a BDTT. This type of HCC was clinically classified as an "icteric type hepatoma" by Lin et al[1] in 1975. Although there are few reports of the clinicopathological features of HCC in patients with BDI, it is well documented that HCC commonly presents with intraductal tumor growth after invading the

if we had considered such a pattern of BDI, its recurrence could have been noticed earlier. Furthermore, more radical surgeries, such as right hepatic lobectomy, should have been indicated as the initial surgery. However, considering the non-invasive biological characteristics of nodular-type HCC, we hesitated to perform a very invasive surgery, such as major hepatectomy as the initial surgery.

Generally, HCC with BDI including a BDTT is thought to have a more infiltrative nature and confer a poorer prognosis than those without BDI.[5,6,8,10,11] However, Kim et al[12] analyzed a large cohort of patients with HCC and BDTT and reported that its impact on survival seemed less prominent than that of other vascular invasions. They also insisted that an aggressive surgical approach, including major liver resection combined with bile duct resection, may result in a reasonably favorable outcome. Fortunately, when we noticed recurrence in the bile duct wall, the recurrent lesion was judged to be somehow resectable. Hence,

we performed right hepatic lobectomy combined with extrahepatic bile duct resection. As a result, R0 resection was achieved, and his condition was favorable without recurrence for 20 months after the second surgery. Considering the present case, this form of BDI may have been constructed with a gentle and slow-growing biological composition in the process of cancer infiltration. However, further accumulation of cases similar to the present case is needed to clarify the clinicopathological features and optimal treatment for this type of HCC with BDI.

4 | CONCLUSIONS

We present a case of recurrent HCC with an unusual form of BDI. It is important to consider that wall thickening in the bile duct adjacent to HCC has the possibility of direct invasion of the bile duct wall.

5 | CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

6 | COMPETING INTERESTS

The authors declare that they have no competing interests.

7 | ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethics approval and consent to participate were not necessary due to the nature of the study.

ACKNOWLEDGMENTS

We would like to thank Editage (www.editage.com) for English language editing.

AUTHORS' CONTRIBUTIONS

TM, TY, TY, HY, and MT performed the surgery. TM drafted and wrote the manuscript under the supervision by MT. HG, DO, AF, and YF participated in its design and coordination. All authors have read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

Not applicable.

ORCID

Taku Matsumoto https://orcid.org/0000-0002-1997-4134

REFERENCES

1. Lin TY, Chen KM, Chen YR, Lin WS, Wang TH, Sung JL. Icteric type hepatoma. *Med Chir Dig*. 1975;4:267-270.
2. Murakami Y, Yokoyama T, Kanehiro T, et al. Successful diagnosis and resection of icteric type hepatocellular carcinoma. *Hepatogastroenterology*. 2003;50:1634-1636.
3. Huang GT, Sheu JC, Lee HS, Lai MY, Wang TH, Chen DS. Icteric type hepatocellular carcinoma: revisited 20 years later. *J Gastroenterol*. 1998;33:53-56.
4. Huang J-F, Wang L-Y, Lin Z-Y, et al. Incidence and clinical outcome of icteric type hepatocellular carcinoma. *J Gastroenterol Hepatol*. 2002;17:190-195.
5. An J, Lee KS, Kim KM, et al. Clinical features and outcomes of patients with hepatocellular carcinoma complicated with bile duct invasion. *Clin Mol Hepatol*. 2017;23:160-169.
6. Kojiro M, Kawabata K, Kawano Y, Shirai F, Takemoto N, Nakashima T. Hepatocellular carcinoma presenting as intrabile duct tumor growth: a clinicopathologic study of 24 cases. *Cancer*. 1982;49:2144-2147.
7. Cabot RC, Mallory TB, Castleman B, Parris EE. Case records of the Massachusetts General Hospital. Case 33441. *N Engl J Med*. 1947;237:673-676.
8. Meng KW, Dong M, Zhang WG, Huang QX. Clinical characteristics and surgical prognosis of hepatocellular carcinoma with bile duct invasion. *Gastroenterol Res Pract*. 2014;2014:604971.
9. Peng BG, Liang LJ, Li SQ, Zhou F, Hua YP, Luo SM. Surgical treatment of hepatocellular carcinoma with bile duct tumor thrombi. *World J Gastroenterol*. 2005;11:3966-3969.
10. Lai ST, Lam KT, Lee KC. Biliary tract invasion and obstruction by hepatocellular carcinoma: report of five cases. *Postgrad Med J*. 1992;68:961-963.
11. Hu XG, Mao W, Hong SY, Kim BW, Xu WG, Wang HJ. Surgical treatment for hepatocellular carcinoma with bile duct invasion. *Ann Surg Treat Res*. 2016;90:139-146.
12. Kim DS, Kim BW, Hatano E, et al. Surgical outcome of hepatocellular carcinoma with bile duct tumor thrombus: A Korea-Japan multicenter study. *Ann Surg*. 2020;271:913-921.

How to cite this article: Matsumoto T, Yoshida T, Yamagishi T, et al. Hepatocellular carcinoma recurrence in the extrahepatic bile duct wall: A case report. *Clin Case Rep*. 2021;9:1561–1565. https://doi.org/10.1002/ccr3.3828