Repeated Hepatectomy for Recurrent Intrahepatic Cholangiolocellular Carcinoma: Report of a Case

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The patient was a 59-year-old female. A liver tumor measuring 10 cm was found in the right hepatic lobe by medical examination of August, 2008 and she underwent extended right hepatectomy in September. Microscopically, the tumor was composed of small cuboidal cells possessing oval nuclei and resembling cholangiole. These formed small tubular structures with fibrous stroma. From a result of histopathological features, a diagnosis of a cholangiolocellular carcinoma was made. She received postoperative adjuvant chemotherapy with gemcitabine and S-1. After that, the patient underwent six partial hepatectomies by August, 2013 for recurrent intrahepatic cholangiolocellular carcinoma. The patient is doing well 7 years after the first hepatectomy. Cholangiolocellular carcinoma is a rare tumor accounting for less than 1% of primary liver cancer, and the clinicopathologic features are not fully understood. Aggressive surgical resection may be one of the choices to assure a good outcome.

Key words: Cholangiolocellular carcinoma, Repeated hepatectomy, Intrahepatic metastasis

INTRODUCTION

Cholangiolocellular carcinoma (CoCC) is rare, acocounting for less than 1% of primary liver cancer. It is suggested that CoCC cells originate from hepatic progenitor or stem cells, but the clinicopathologic features are not fully understood. In this report, we present a patient in whom recurrence was detected in the remnant liver 6 times after the first hepatectomy for CoCC, but additional hepatectomy was performed 6 times, achieving long survival.

CASE REPORT

A 59-year-old female was referred to our hospital in August, 2008 after the ultrasonographic detection of a tumor measuring 10 cm in the right hepatic lobe. She did not have any symptoms, but there was a 10-kg weight loss during a period of 2 years. She had a history of cholelithiasis, but had not undergone operation. No excessive alcohol consumption. Laboratory data on admission were as follows; AST 32U/l, ALT 37 U/l, ALP 531 U/l, serum albumin 4.2 g/dl, and total bilirubin 0.5 mg/dl. According to the Child-Pugh classification, the stage was evaluated as A, and the grade of liver damage was assessed as A. The patient was negative for hepatitis B surface antigen and hepatitis C virus antibody. The levels of tumor markers were slightly increased as follows; cancer-associated carbohydrate antigen 19−9 (CA 19−9) 32.1 U/ml and protein induced by vitamin K absence or antagonist-II (PIVKA-II) 45 mAU/ml. The levels of carcinoembryonic antigen (CEA) and serum alpha-fetoprotein (AFP) were normal. Abdominal ultrasonography revealed a low-echoic mass measuring 103 x 73 mm, with a clear border. Doppler ultrasonography showed abundant blood flow signals. Contrast-enhanced abdominal computed tomography (CT) demonstrated a tumor measuring 106 x 96 x 65 mm, with a clear border. In the arterial phase, the tumor margin was lightly stained in a patchy pattern (Fig. 1a). In the equilibrium phase, enhancement effects were protracted at the tumor center (Fig. 1b). Abdominal magnetic resonance imaging (MRI) on T1-weighted images, the signal intensity of the tumor was lower than that of the liver (Fig. 2a). On T2-weighted images, it was slightly higher than that of the liver (Fig. 2b). Based on these imaging findings, it was necessary to differentiate intrahepatic cholangiocarcinoma (ICC), hepatocellular carcinoma (HCC), sclerotic HCC, and mixed type liver cancer.

She underwent extended right hepatectomy in September, 2008. Although the sampling of a hepatoduodenal ligament lymph node and that around the common hepatic artery was performed, there was no metastasis. The gross findings revealed a white solid nodular mass measuring 100 x 100 x 95 mm, with no capsule formation and an irregularly shaped margin (Fig. 3).

Microscopically, the tumor was composed of atypical cuboidal cells possessing enlarged round nuclei and eosinophilic cytoplasm. These formed irregular tubular structures with fibrotic stroma (Fig. 4a). Around the tumor, there was no fibrous capsule, and the continui-

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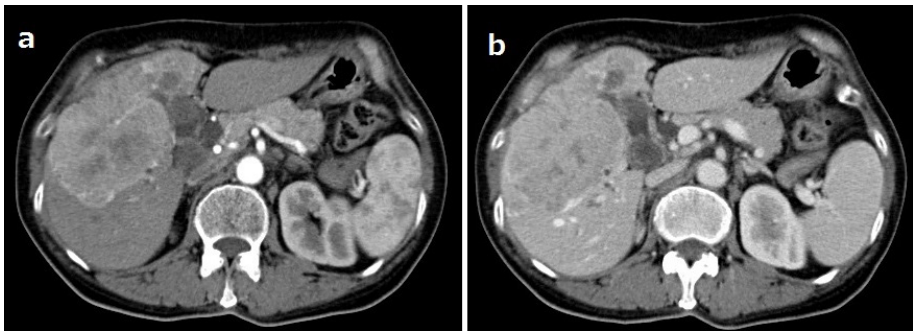

Fig. 1 Abdominal contrast-enhanced computed tomography
In the arterial phase, the tumor margin was lightly stained in a patchy pattern (a). In the equilibrium phase, enhancement effects were protracted at the tumor center (b).

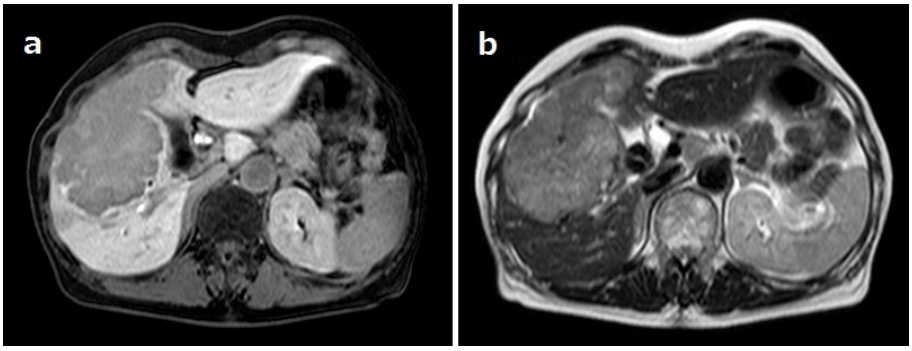

Fig. 2 Abdominal magnetic resonance imaging
The tumor was shown low intensity on T1-weighted images (a) and high intensity on T2-weighted images (b).

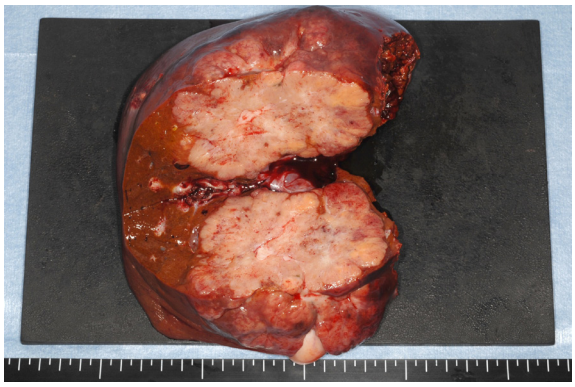

Fig. 3 The gross findings of the primary tumor
The tumor reveals a white yellowish nodular mass with no capsule formation.

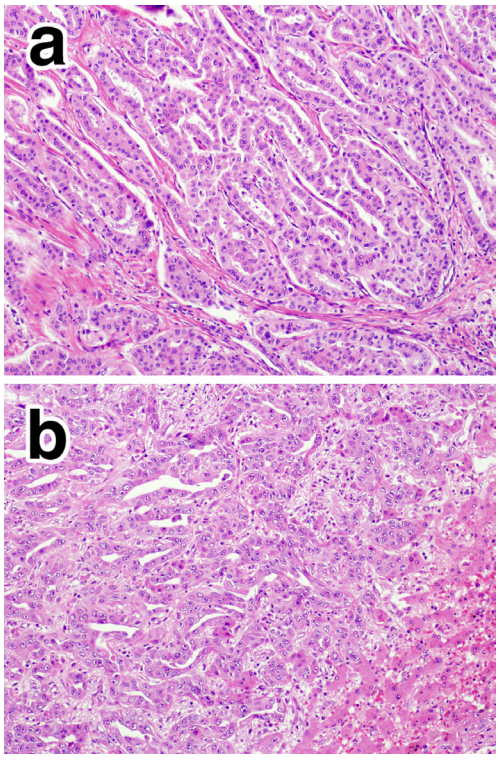

Fig. 4 Histopathological findings of the primary tumor (HE stain)
The tumor was composed of atypical cuboidal cells possessing enlarged round nuclei and eosinophilic cytoplasm. These formed irregular tubular structures with fibrotic stroma (a). The continuity of the peripheral hepatic cords with tumor cells was partially noted (b).

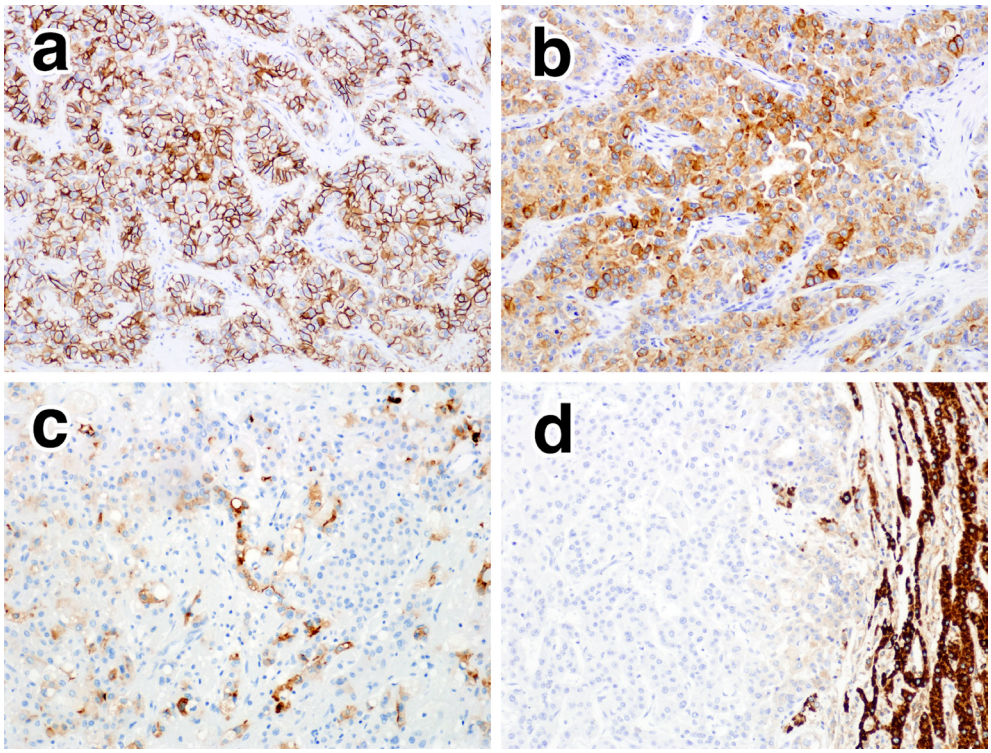

Fig. 5 Immunohistochemical findings of the primary tumor
The tumor cell is positive for CD56 (a), CK19 (b), EMA (c) but negative for HepPar-1 (d).

ty of the peripheral hepatic cords with tumor cells was partially noted (Fig. 4b). On immunohistochemical examination, the tumor was positive for CD56 (Fig. 5a), cytokeratin 7 (CK7), cytokeratin 19 (CK19) (Fig. 5b), mucin core protein 1 (MUC-1), epithelial membrane antigen (EMA) (Fig. 5c), and negative for hepatocyte paraffin 1 (HepPar-1) (Fig. 5d). Based on the histopathological and immunohistochemical findings, this tumor was diagnosed as CoCC.

There were no complications, and the patient was discharged from our hospital on postoperative day 22. The patient received postoperative adjuvant chemotherapy with gemcitabine and S-1. In November, 2008, she noticed a mass of the left breast. Detailed examination led to a diagnosis of breast cancer. In February, 2009, partial left mastectomy was performed. On histopathological findings, the tumor was evaluated as T1N0M0, stage I, and Luminal A type. Letrozole was orally administered. In March, 2010, CT demonstrated a solitary nodular lesion measuring 20 mm in segment 4 of the remnant liver (Fig. 6a), suggesting recurrent intrahepatic CoCC.

In March, 2010, partial hepatectomy was performed. There was no lymph node metastasis or peritoneal dissemination. The tumor measured approximately 20 mm, being white and solid. Histopathological findings were similar to those at the time of the first hepatectomy, leading to a diagnosis of recurrent intrahepatic CoCC. On immunohistochemical examination, as the tumor was negative for estrogen receptor (ER) and progesterone receptor (PgR), there was not the possibility of liver metastasis from breast cancer.

There were no complications, and the patient was discharged on postoperative day 11. In September, 2010, CT demonstrated a solitary nodular lesion measuring 10 mm in segment 4 of the remnant liver (Fig. 6b). The course suggested recurrent intrahepatic CoCC, and partial hepatectomy was performed. Histopathological findings were similar to those at the time of the first hepatectomy, leading to a diagnosis of recurrent intrahepatic CoCC. Subsequently, recurrent intrahepatic CoCC was detected in segment 2/3 and segment 2 in March, 2011, in segment 1/3, segment 2, and segment 3 in August, 2011, in segment 2 in February, 2012, and in segment 3 in August, 2013 (Fig. 7a to 7d). Every time it was detected, partial hepatectomy was performed, and there were no complications. Histopathological findings of all lesions were similar to those at the time of the first hepatectomy, leading to a diagnosis of recurrent intrahepatic CoCC. The patient is presently still alive and well 7 years after the first hepectomy for a primary CoCC, since August, 2013, there has been no recurrence.

DISCUSSION

Steiner and Higginson first reported CoCC in 1959 [1]. As this tumor has cells that may differentiate into hepatocytes or bile duct cells, the involvement of the hepatic progenitor or stem cells is suggested as its origin. CoCC has been regarded as a subtype of ICC, but its characteristics may differ from those of ICC. Therefore, CoCC is independent from ICC and is reclassified as a type of primary liver cancer according to the Liver Cancer Study Group of Japan [2]. However, histopathologically, there are no diagnostic criteria for CoCC, and there are differences in diagnosis among pathologists or institutions.

CoCC frequently develops in middle-aged or elderly persons. As background factors, most patients have chronic liver diseases, such as liver cirrhosis [3]. As

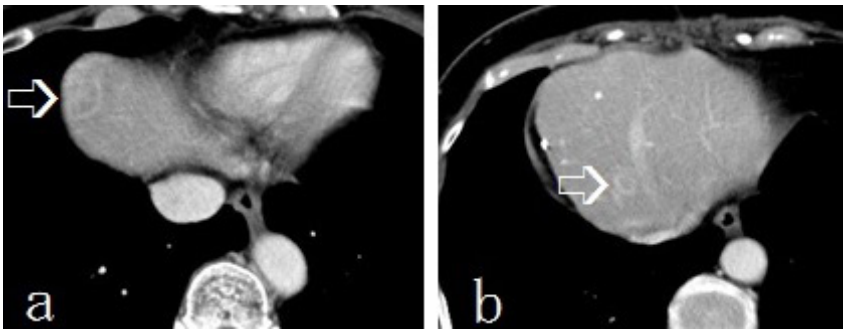

Fig. 6 Abdominal enhanced computed tomography of the recurrent tumor in the remnant liver
It showed a recurrent tumor measuring 20 mm in segment 4 (a), a recurrent tumor measuring 8 mm in segment 4 (b).

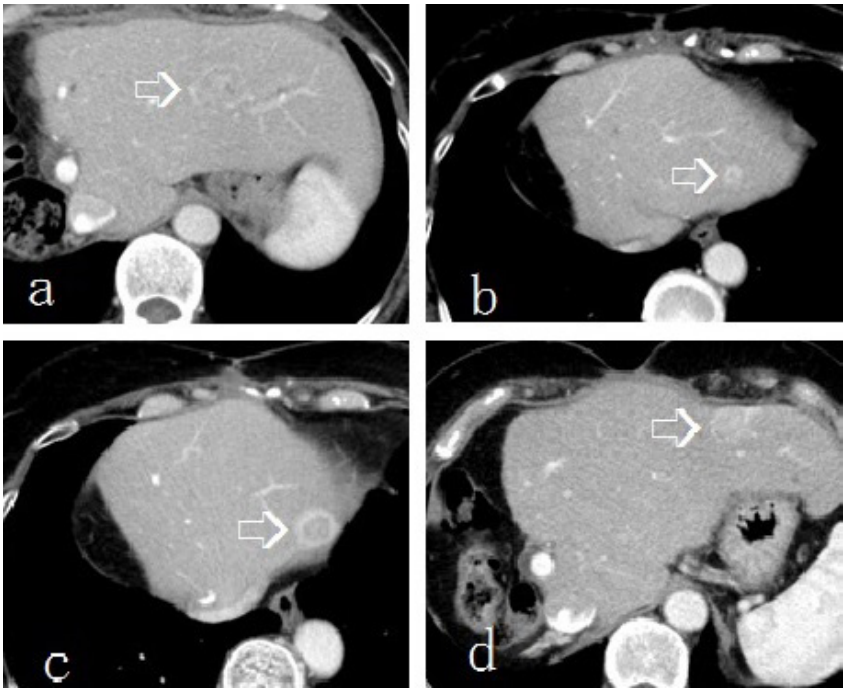

Fig. 7 Abdominal enhanced computed tomography of the recurrent tumor in the remnant liver
It showed a recurrent tumor in segment 3 (a), segment 2 (b), segment 2 (c), segment 3 (d).

diagnostic imaging findings, CoCC is visualized as low-echoic area on ultrasonography and a low-attenuation area on plain CT. In the early phase of contrast enhancement, the nodular margin is contrast-enhanced. In the late phase, the nodular center is darkly stained, and enhancement effects are protracted in many cases. However, in some cases, it is darkly stained in the early phase, whereas it is not contrast-enhanced in others. On T1-weighted MRI images, a low signal intensity is often detected, and, on T2-weighted images, a high signal intensity is often detected [4]. Therefore, it is difficult to make a diagnosis of CoCC without histopathological findings.

The gross findings of CoCC resemble those of ICC, most lesions are white to light yellow, hard and nodular [5]. Histopathologically, less atypical cancer cells resembling the cholangiole or Hering's canal comprise a minor ductal structure, and irregularly proliferate like anastomosis [1, 6]. At the end of the proliferative site, many cancer cells replace hepatocytes, and proliferate. The volume of fibrous stroma is abundant, and there is no mucus secretion by tumor cells [7]. CoCC alone is rarely detected, and ICC- or HCC-like findings are concomitantly present in the same tumor in many cases [6]. On immunohistochemical findings, the CoCC cells are positive for cytokeratin 8 (CK8), cytokeratin 9 (CK9), and cytokeratin 19 (CK19), whereas it is negative for cytokeratin 20 (CK20) and Hep1, as markers of hepatocytes, in most cases [8]. Although the staining reactions of CoCC are similar to those of ICC, Yamada *et al.* [9] reported that there was a difference in the morphology of EMA expression. ICC cells were cytoplasmic positive for EMA, whereas CoCC cells were membranous positive for EMA. Although such characteristics are observed, accurate histopathological diagnosis is difficult in many cases.

As the invasion of CoCC is less marked than that of primary liver cancer or ICC, the prognosis is relatively favorable [5]. However, long-term follow-up was impossible in many reported patients, it remains to be clarified.

To our knowledge, the number of patients who underwent the additional resection of recurrent lesion after curative hepatectomy for CoCC is 5, including our case[3, 10–12]. In all patients, recurrence was detected in the remnant liver, and the interval from the first hepatectomy until recurrence ranged from 7 months to 3 years. Two patients [3, 10] died of recurrence 3 years, and 1 year and 1 month after the first operation, respectively. Yamamoto *et al.* [11] reported 1 patient achieving 4-year survival after additional hepatectomy. There were no patients who repeatedly underwent additional hepatectomy for recurrent intrahepatic CoCC, as demonstrated in our patient.

Only a few case reports on CoCC have been published, and the clinicopathologic features are unclear. However, the results suggest that survival is prolonged by repeated hepatectomy for recurrent intrahepatic CoCC after curative hepatectomy. In the present case, CoCC was detected, and hepatectomy for recurrent intrahepatic CoCC was repeatedly performed, achieving 7-year survival, which is rare. Diagnosis and prognosis remain to be clarified. In the future, a large number of patients should be accumulated.

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