Int Surg 2015;**100:**1111–1116
DOI: 10.9738/INTSURG-D-14-00215.1

Case Report

Giant Cholangiolocellular Carcinoma With Early Recurrence That Was Difficult to Distinguish From Cholangiocellular Carcinoma: Report of a Case

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Cholangiolocellular carcinoma (CoCC) is a rare type of malignant liver tumor derived from hepatic stem cells, which exist in the canals of Hering. However, the characteristics of CoCC have not been clarified. In general, CoCC is associated with a better prognosis than cholangiocellular carcinoma (CCC). Here, we report a case of giant CoCC, which was difficult to distinguish from CCC and showed early recurrence and necrosis inside the tumor. A 59-year-old man was diagnosed with CCC based on preoperative imaging. The diameter of the tumor was approximately 14 cm, and he subsequently underwent extended right lobectomy of the liver. Histopathologic analysis revealed that tumor cells proliferated and replaced the surrounding normal liver cell cords in front of the tumor. Furthermore, the tumor cells were positive for cytokeratin 19 and epithelial membrane antigen. Epithelial membrane antigen staining pattern was positive on the membranous area of the lumen. Therefore, the tumor was diagnosed as CoCC. Although adjuvant chemotherapy was performed, intrahepatic recurrence occurred at 4 months after surgery. We present here the novel characteristics of CoCC that show early recurrence and necrosis within the tumor. These characteristics have not previously been reported in patients with CoCC.

Key words: Cholangiolocellular carcinoma – Recurrence – Giant tumor – Cholangiocarcinoma – Necrosis – Stem cells

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Cholangiolocellular carcinoma (CoCC) is a rare malignant tumor of the liver. The incidence of CoCC was reported to be 0.56% in patients with resected primary liver cancer.[1] Although CoCC was first described by Steiner and Higginson in 1959,[2] the histogenesis of CoCC was unclear for many years; however, recent studies have shown that CoCC originates from hepatic stem cells, which exist in the canals of Hering.[3–5] Hepatic stem cells have the potential to differentiate into both hepatocytes and cholangiocytes.[6] Therefore, although CoCC was formerly categorized as a subtype of cholangiocellular carcinoma (CCC), it is now categorized as combined hepatocellular-cholangiocarcinoma with stem cell features, cholangiolocellular subtype, in the latest World Health Organization classification. Because of the low incidence of CoCC, the characteristics of this tumor type have not yet been fully elucidated.

In this report, we present a case of giant CoCC that was difficult to distinguish from CCC and showed early recurrence and necrosis. These characteristics have not been reported previously in patients with CoCC.

Case Report

A 59-year-old man was admitted for right hypochondrial pain. A giant tumor in the right lobe of the liver was pointed out by computed tomography (CT). Laboratory data were almost normal, but alkaline phosphatase and γ-glutamyl transpeptidase levels were elevated slightly. The levels of tumor markers, such as carcinoembryonic antigen and carbohydrate antigen 19-9, were elevated (carcinoembryonic antigen, 53.7 ng/mL; carbohydrate antigen 19-9, 6752 U/mL). Hepatitis B virus (HBV) surface antigen (HBs-Ag) was negative, but HBV surface antibody (HBs-Ab) and core antibody (HBc-Ab) were positive. Hepatitis C virus (HCV) antibody was negative (Table 1).

Table 1 Laboratory data

	Value
WBC count, /μL	9300
RBC count, × 10^4/μL	425
Hb, g/dL	12.9
Hct, %	38.8
Plt, × 10^4/μL	17.3
AST, IU/L	28
ALT, IU/L	17
LDH, IU/L	279
ALP, IU/L	484
g-GTP, IU/L	96
Total bilirubin, mg/dL	0.4
TP, g/dL	7.2
ALB, g/dL	3.7
BUN, mg/dL	14
Cre, mg/dL	0.64
Na, mEq/L	141
K, mEq/L	4.3
Cl, mEq/L	105
Ca, mg/dL	9.7
PT, %	93
APTT, s	31.2
CEA, ng/mL	53.7
CA19-9, U/mL	6752
HBs-Ag	−
HBc-Ag	+
HBc-Ab	+
HCV-Ab	−

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; Cre, creatinine; g-GTP, c-glutamyl transpeptidase; Hb, hemoglobin; Hct, hematocrit; LDH, lactate dehydrogenase; Plt, platelets; PT, prothrombin time; RBC, red blood cell; TP, total protein; WBC, white blood cell.

CT revealed a giant tumor in the right lobe of the liver, measuring approximately 14 cm in diameter. In the early phase, the tumor was enhanced at the periphery, and the margin of the tumor was unclear (Fig. 1a). Vessel penetration into the tumor was observed from the early phase to the portal phase (Fig. 1d). Additionally, from the portal phase to the delayed phase, the tumor exhibited homogeneous enhancement relative to the normal liver (Fig. 1b). The inside of the tumor did not exhibit enhancement. And the infiltration to the main portal vein was not evident (Fig. 1c). Capsules showing delayed peripheral enhancement, similar to hepatocellular carcinoma, were not detected. CT also revealed para-aortic lymph node swelling (Fig. 1e). On magnetic resonance imaging, the tumor showed low-intensity T1-weighted images and various high-intensity T2-weighted images. 18F-fluorodeoxyglucose positron emission tomography revealed uptake of 18F-fluorodeoxyglucose within the tumor. The standardized uptake value maximum was 12.8. However, 18F-fluorodeoxyglucose positron emission tomography did not show increased uptake in the para-aortic lymph node, which was detected by CT scan (Fig. 1f).

We also performed enhanced abdominal ultrasonography (US) using Sonazoid (perfluorobutane, Daiichi-Sankyo, Tokyo, Japan). The tumor exhibited a heterogeneous hypoechoic area in pre-enhanced US, and the border was unclear. In enhanced US, the

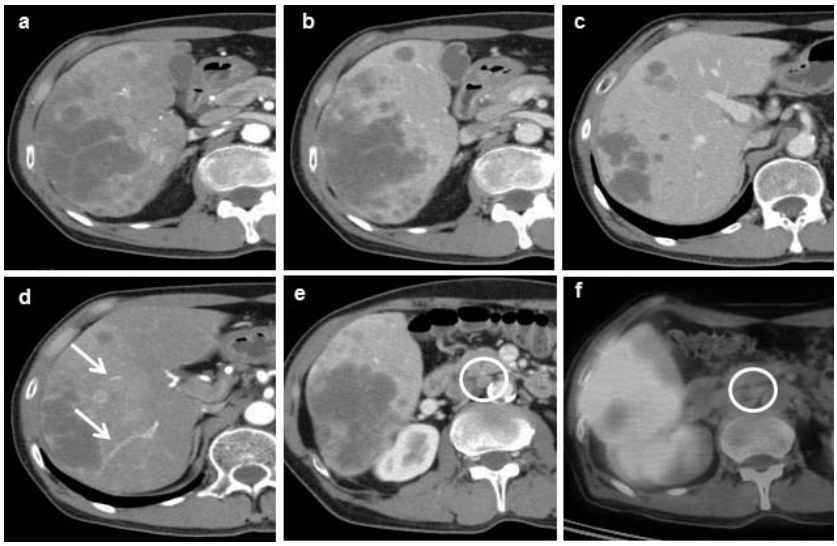

Fig. 1 CT findings. (a) The tumor was enhanced at the periphery during the early phase. (b) From the portal phase to the delayed phase, the tumor exhibited homogeneous enhancement relative to the normal liver. The inside of the tumor was not enhanced. (c) The infiltration to the main portal vein was not evident. (d) Vessel penetration into the tumor was observed from the early phase to the portal phase (arrows). (e and f) Para-aortic lymph node swelling was observed (circle), but did not exhibit uptake of 18F-fluorodeoxyglucose.

tumor exhibited peripheral enhancement in the arterial phase, during which defect of contrast was observed on the inside of the tumor (Fig. 2a). The tumor lesion gradually became hypoechoic relative to the normal liver parenchyma and revealed the defect of enhancement during the Kupffer phase (Fig. 2b).

Based on these findings, we diagnosed the liver tumor as CCC prior to operation. We planned to perform extended right lobectomy of the liver. Therefore, we carried out right portal vein embolization before operation, anticipating enlargement of the residual liver. One month after embolization, the residual liver volume increased nearly 10%, and there were no other metastases or intrahepatic lesions present. Therefore, extended right lobectomy of the liver and lymph node dissection were performed. Because there was no lymphadenopathy on the hepatoduodenal ligament and there was no infiltration toward the extrahepatic bile duct, bile

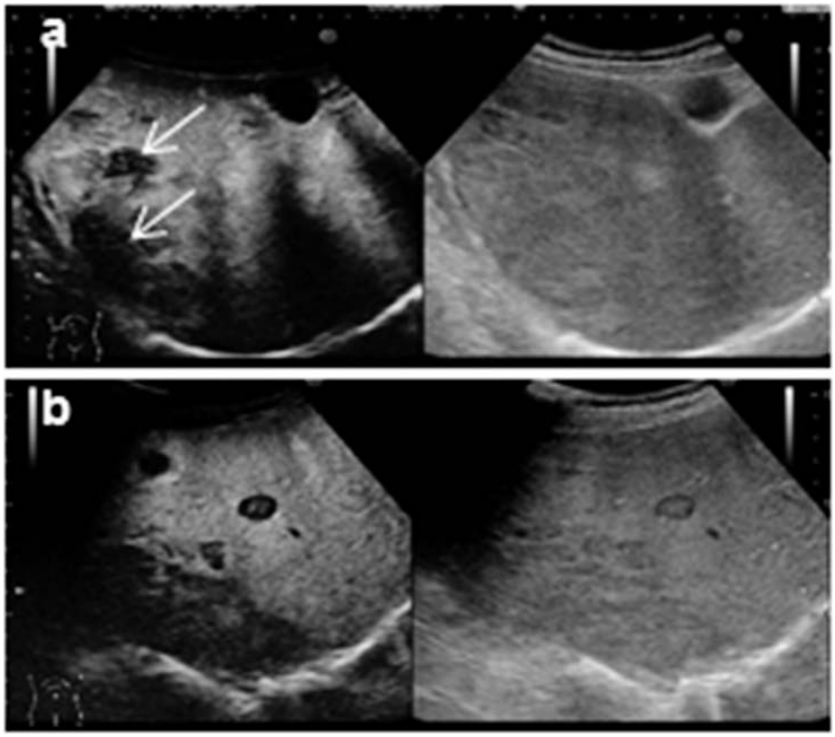

Fig. 2 US using Sonazoid findings. (a) The tumor appeared to have peripheral enhancement during the arterial phase. And defect of contrast was observed inside the tumor (arrows). (b) The tumor clearly exhibited a lack of enhancement during the Kupffer phase.

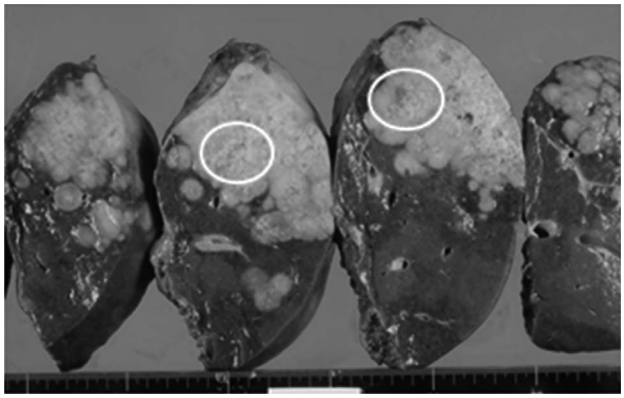

Fig. 3 The gross appearance of tumor was white in color, and the tumor measured 14 × 10 × 8 cm. Necrotic lesions were observed inside the tumor (circles).

duct resection was not performed. Because of the observed para-aortic lymph node swelling in preoperative CT findings, we removed the lymph node and confirmed that there were no additional malignancies by intraoperative pathologic diagnosis before right lobectomy.

The gross appearance of the tumor was white in color; it resembled contiguous multinodular type; it measured 14 × 10 × 8 cm; and it had irregular margins without a capsule. Additionally, we observed necrotic lesions inside the tumor (Fig. 3). Histopathologic findings revealed that the tumor was composed of small glands showing anastomosing patterns resembling antlers. Tumor cells had slightly eosinophilic cytoplasm, and round nuclei with clear nucleoli. Moreover, the tumor cells proliferated and replaced the surrounding normal liver cell cords in front of the tumor (Fig. 4a). These cells were immunohistologically positive for cytokeratin 19 (CK19) and negative for hepatocyte paraffin-1 (Fig. 4b and 4c). The staining pattern for epithelial membrane antigen was positive on the membranous area of the lumen (Fig. 4d), resembling a membranous pattern. Thus, we diagnosed this tumor as CoCC. In addition, vascular invasion, especially portal vein invasion, was strongly positive (Fig. 4e), and lymph nodes on the porta hepatis were positive for metastasis. Although biliary invasion was also positive, the margins of resection were negative. His postoperative course was uneventful, and the patient was discharged 16 days after operation.

Although an appropriate adjuvant therapy for CoCC has not been established, we performed chemotherapy with gemcitabine and cisplatin. However, follow-up CT and magnetic resonance imaging at 4 months after surgery showed multiple intrahepatic recurrences. Therefore, the patient continued chemotherapy with gemcitabine plus S-1.

Discussion

Following the recognition of CoCC in the latest World Health Organization classification, reports of CoCC have been increasing gradually over time and are expected to continue to increase in the coming years. Therefore, the clinicopathologic features of CoCC are gradually becoming clear. In previous reports, patients with CoCC have been shown to have chronic liver injury, such as HBV or HCV

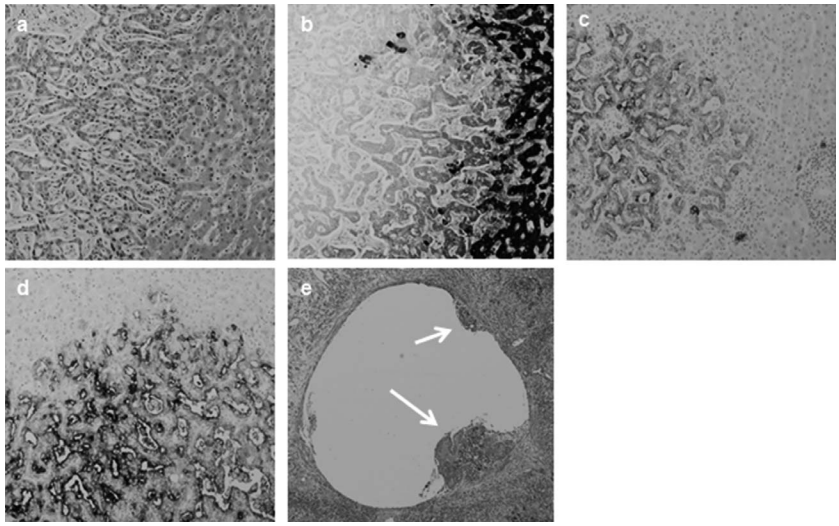

Fig. 4 Histopathologic findings. (a) The tumor was composed of small glands showing antlerlike anastomosing patterns. The tumor cells proliferated and replaced the surrounding normal liver cell cords in front of the tumor. The tumor cells were negative for hepatocyte paraffin-1 (b) and positive for CK19 (c). (d) Epithelial membrane antigen was positive on the membranous area of the lumen. (e) The tumor cells were observed in the portal vein (arrows).

infections, alcoholism, or hemochromatosis, with higher frequency than patients with CCC.[1,3,7,8] This is thought to result from the observation that hepatic stem cells are activated during chronic liver injury. Our patient was negative for HBs-Ag and HCV-Ab, but HBs-Ab and HBc-Ab were positive. Therefore, we suspected that our patient had been infected with HBV in the past.

In many cases of CoCC, the tumor size is less than 10 cm in diameter.[3,4,9–13] However, our patient's tumor was 14 cm in diameter; therefore, this was the largest tumor described in the literature. It is unclear why so many cases exhibit small tumors. However, one report also described a patient with CoCC that developed 4 years after the patient was diagnosed with hemangioma.[10] Therefore, the growth speed of CoCC may be relatively slow. Additionally, although the absence of necrosis inside of the tumor is considered to be characteristic of CoCC,[3] we observed necrosis in the center of the tumor in our patient. Two previous cases have reported CoCC with necrosis inside the tumor.[14,15] In one case, the tumor was greater than 10 cm, whereas in the other case, the tumor was only 6 cm in diameter; both cases exhibited rapid progression. These previous studies suggested that necrosis may develop within the tumor if the tumor becomes larger and exhibits rapid growth.

A few reports have described imaging findings in patients with CoCC.[11,16,17] On enhanced CT, CoCC revealed early enhancement and delayed washout, similar to hepatocellular carcinoma, or ringed enhancement at the periphery during the early phase and persistent enhancement during the delayed phase, similar to CCC. In a previous study, lesions showing contrast enhancement during the early phase exhibited abundant cellularity, whereas the area of persistent enhancement during the delayed phase exhibited abundant fibrous stroma.[18] Thus, CT findings in CoCC reflected the histologic features of the tumor. Enhanced US using Sonazoid has been infrequently reported compared with CT findings. According to a prior report,[19] CoCC shows whole-tumor enhancement in the arterial phase, becomes progressively hypoechoic relative to the normal liver parenchyma, and shows defect of enhancement during the Kupffer phase. However, our patient exhibited peripheral enhancement during the arterial phase and defect of contrast inside the tumor, likely due to necrosis. Thus, CoCC can yield various imaging findings, and few studies have confirmed the presence of characteristic imaging findings. Therefore, it is thought to be difficult to diagnose CoCC preoperatively. Furthermore, there are reports that CoCC is composed of three different areas histologically—CoCC, hepatocellular carcinoma–like, and CCC-like[3,20]—which supported the hypothesis that CoCC is derived from hepatic stem cells. However, because of the heterogeneous distribution of cells in CoCC, needle biopsy may yield different results depending on the region of the tumor that is biopsied. Sasaki *et al*[21] have described the prevalence of subtypes in combined hepatocellular-cholangiocarcinoma. In the report, although the prevalence of CoCC subtype was 69.8% in all combined hepatocellular-cholangiocarcinomas, each subtype was observed in various amounts and combinations. Thus, even if the tumor is diagnosed as hepatocellular carcinoma by biopsy, when it looks like CCC radiographically, it is necessary to consider the possibility of CoCC, which is a subtype of combined hepatocellular-cholangiocarcinoma.

An appropriate therapy for CoCC has not been established. However, the prognosis of CoCC is improved after resection, compared with that of CCC.[22] Therefore, in resectable CoCC surgical operation is the most effective treatment, similar to other types of primary liver cancer. In contrast, CoCC tumors with a diameter greater than 4 cm show higher recurrence rates compared with smaller CoCC tumors.[3] Additionally, intrahepatic lesions are the most frequent recurrence for CoCC,[3,22] most likely due to the high frequency of portal vein invasion in CoCC histologically. Our patient showed early intrahepatic recurrence because of the large size of the tumor and the prominent portal vein invasion. Therefore, we would expect our patient to have a high risk of recurrence. In advanced or recurrent cases, chemotherapy is often performed. Because CoCC is associated with expression of cholangiocyte markers, such as CK7 and CK19, chemotherapy regimens generally used for CCC are expected to be effective.[7,23] Although we also performed chemotherapy with gemcitabine plus cisplatin, according to the ABC-02 trial,[24] because of the advanced stage and positivity for massive vascular invasion and lymph node metastasis in our patient, we unfortunately could not prevent recurrence. Further investigations with greater numbers of patients are required in order to establish effective chemotherapeutic regimens for CoCC.

We presented here a case of giant CoCC; this was the largest CoCC case reported to date, and it exhibited necrosis within the tumor and early recurrence. These characteristics were different from those reported previously. Indeed, the clinicopath-

ologic characteristics of CoCC have not yet been clarified. Therefore, analysis of additional cases is required to establish the characteristics of CoCC.

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