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A case of cholangiolocellular carcinoma featuring intratumoral hepatic artery penetration: A case report

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ABSTRACT

INTRODUCTION: Cholangiolocellular carcinoma (CoCC) is thought to originate from hepatic stem cells. Its clinical characteristics, including radiological and prognostic factors, remain unclear.

PRESENTATION OF CASE: A 79-year-old woman with hypertension was admitted to our hospital after abnormal tumor marker levels were detected during an annual physical examination. Her laboratory data results were within normal range, and she was classified as Child-Pugh A. Enhanced computed tomography revealed a tumor located on the left side of the liver, with a maximum size of 60 mm. The tumor showed heterogeneously enhancing edges in the arterial phase, while prolonged tumor enhancement was detected in the delayed phase. Tumor penetration by the left hepatic artery was evident, whereas the left portal vein was invaded by the tumor. The preoperative diagnosis was cholangiolocellular carcinoma. Left hepatectomy and cholecystectomy were performed with no postoperative complications; the final diagnosis was CoCC. Multiple liver metastases appeared 6 months after surgery; the patient is now receiving systematic chemotherapy.

DISCUSSION: While portal vein penetration into CoCCs has been reported, the same is not true of the hepatic artery; therefore, this case illustrates a unique tumor growth pattern.

CONCLUSION: A unique growth pattern as well as a large primary tumor may contribute to earlier recurrence.

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1. Introduction

Cholangiolocellular carcinoma (CoCC) is a rare type of liver cancer [1,2], and was first reported by Steiner and Higginson in 1959 [1]. CoCC is derived from the Canals of Hering, or cholangioles, where hepatic progenitor cells (HPCs) are located [3]. HPCs have the potential to differentiate into hepatocytes and cholangiocytes [4], and expression of the HPC markers CD56, CD13, and epithelial cell adhesion molecule (EpCAM) are characteristic of CoCC [5].

It is difficult to diagnose CoCC preoperatively without histopathological analysis; its radiological attributes are very similar to those of cholangiocellular carcinoma (CCC) and malignant lymphoma, which are characterized by tumor enhancement patterns and a specific shape on contrast-enhanced computed tomography (CT) [6]. Vascular penetration into the tumor, with no

capsule present, is one of the notable characteristics of CoCC [7]. The disease has a post-curative surgery prognosis that lies between hepatocellular carcinoma (HCC) and CCC, in terms of favorable outcomes [8,9].

We present a patient with CoCC who underwent curative surgery, although multiple liver recurrences were observed 6 months later. We also conduct a literature review on CoCCs. This work has been reported in line with the SCARE criteria [10].

2. Presentation of case

The patient was a 79-year-old woman with hypertension; she had no relevant medical history and did not abuse alcohol. Elevated carbohydrate antigen 19-9 (CA19-9) was noted during an annual medical examination, and she was admitted to the Department of Surgery at our institution. Her physical examination was normal; however, her levels of tumor markers were as follows: CA19-9, 370 U/mL (normal, <37.0 U/mL); carcinoembryonic antigen, 1.6 ng/mL (normal, <5.5 ng/mL); alfa-fetoprotein, 2.2 ng/mL

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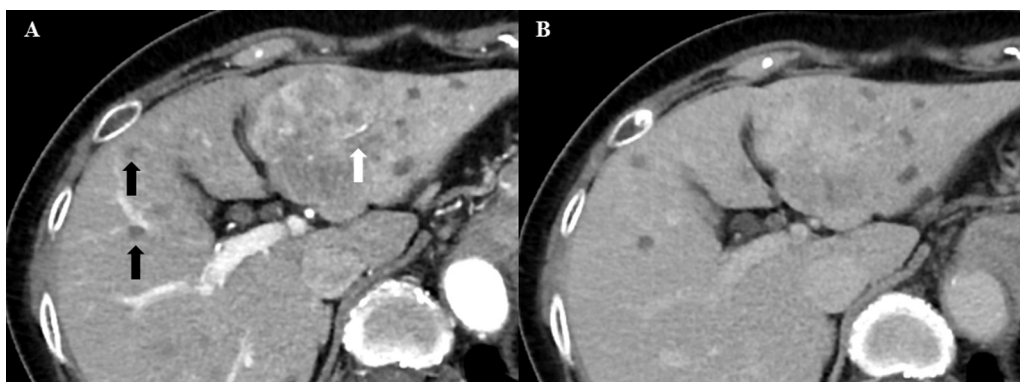


Fig. 1. Preoperative computed tomography. (A) The tumor in the left hepatic lobe showed enhancement from its periphery, with penetration of the hepatic artery and the dilatation of the peripheral biliary duct in the arterial phase (white arrow). Liver cysts were observed in segments 5 (black arrow). (B) Tumor enhancement was prolonged in the equilibrium phase.

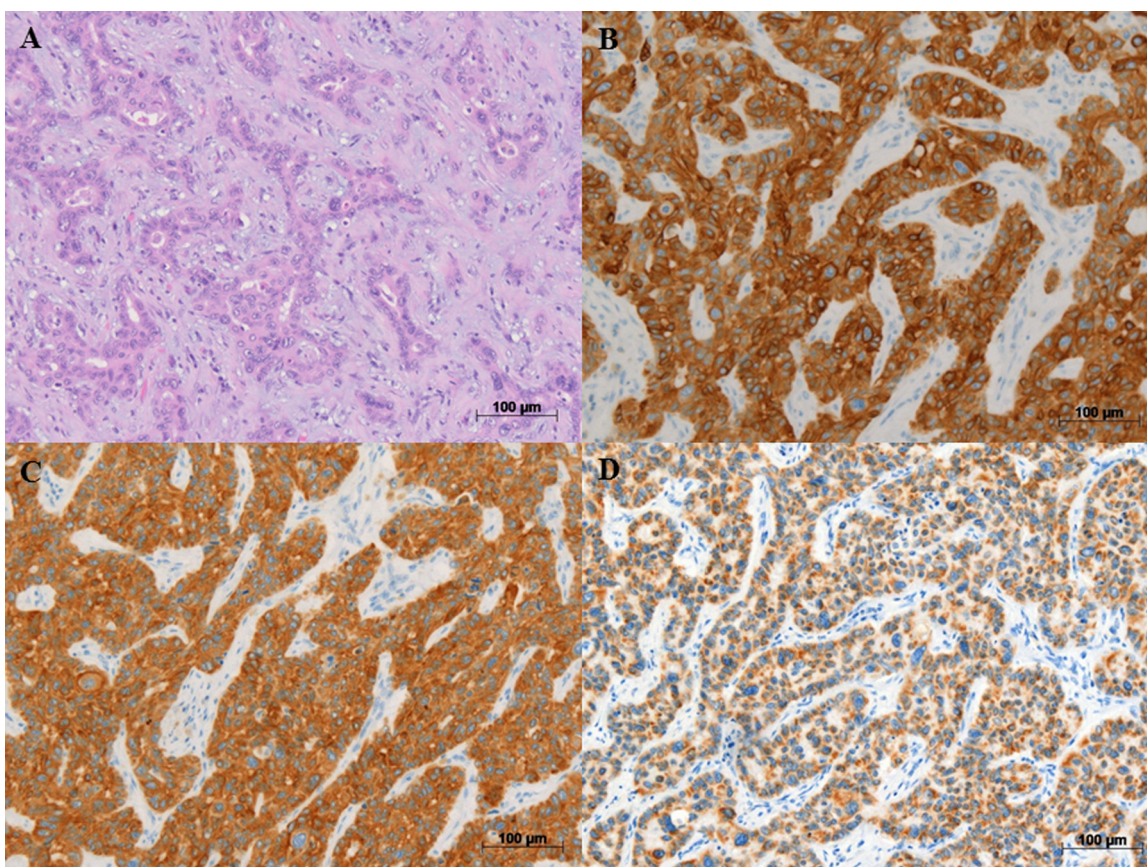


Fig. 2. Immunohistochemical findings of the tumor. (A) Hematoxylin and eosin staining: The tumor was composed of small glands showing antler-like and anastomosing patterns with abundant fibrous stroma. The tumor was positive for cytokeratin (CK) 7 (B), CK19 (C), and epithelial cell adhesion molecule (D).

(normal, <10.0 ng/mL); and protein induced vitamin K absence or antagonists-II, 20 mAU/mL (normal, <40 mAU/mL). Hepatitis virus markers were all negative. Her laboratory data indicated a Child-Pugh A classification. Contrast-enhanced CT revealed a tumor located in segment 4 measuring 60 mm (at most) with an unclear border. In early-phase imaging, the tumor showed enhancement at the tumor periphery; this was prolonged on late-phase imaging (Fig. 1). With magnetic resonance imaging (MRI), the tumor showed low and high intensities on T1- and T2-weighted images, respectively. This enhancement was washed out in the hepatocellular phase. Interestingly, the hepatic artery was observed penetrating the tumor on both CT and MRI. The patient's preoperative

diagnosis was CCC following which left hepatectomy and cholecystectomy were performed. The duration of the surgery was 262 min, and the bleeding volume was 200 mL. Macroscopically, the tumor in segment 4 of the liver was a 60 × 55 × 50 mm well-defined yellowish-white lesion. Histological examination revealed that the proliferating tumor cells replaced the surrounding normal tissue, and were composed of antler-like and anastomosing patterns with abundant fibrous stroma. There was no invasion into the vessels or lymph ducts. Immunohistochemical examination revealed positive expression of cytokeratin (CK) 7, CK19, and EpCAM (Fig. 2). Hence, the final diagnosis was CoCC.

Table 1
Reported clinicopathological variables of patients with CoCC following curative surgery.

Author	Age	Sex	Etiology	CEA (ng/L)	CA19-9 (U/mL)	Tumor location	Maximal tumor size (mm)	Surgery	CK7/19	EpCAM	Postoperative therapy	Prognosis
Matsuda	70	M	HCV	Normal	Normal	S7	22	Medial and posterior segmentectomy without LD	ND/+	(–)	ND	Alive for 30 months without recurrence
Kanamoto	71	M	HCV	Normal	Normal	Right lobe	15	Partial hepatectomy without LD	+/-	ND	ND	Alive for 12 months without recurrence
Kadono	45	F	(–)	Normal	Normal	S4	75	Partial hepatectomy without LD	+/+	ND	ND	Alive for 12 months without recurrence
Ishii	59	M	HBV	53.7	6752	Right lobe	140	Extended right lobectomy with LD	ND/+	ND	ACT: GEM, cisplatin GEM, S-1	Alive for 4 months with multiple liver metastasis
Jung	62	M	Alcohol	2.2	12.1	Right lobe	50	Right lobectomy without LD	ND/+	(+)	ND	ND
Tomioku	59	F	(–)	Normal	32.1	Right lobe	100	Extended right lobectomy without LD	+/+	ND	ACT: GEM, S-1 Additional hepatectomy	Alive for 84 months with intrahepatic recurrence
Yoh	72	M	HCV	ND	ND	S6/8	50	Extended right lobectomy without LD	+/+	ND	ND	Died after 65 days with multiple liver metastases
Suzumura	45	M	HBV	ND	ND	S7	23	Posterior segmentectomy without LD	+/+	(–)	ND	Died after 20 months with lymph node recurrence
Sakane	56	F	(–)	ND	ND	Right lobe	16	Partial hepatectomy without LD	+/+	ND	ND	ND
Present case	79	F	(–)	1.6	370	S4	60	Left lobectomy without LD	+/+	(+)	ACT: S-1 GEM	Alive for 10 months with multiple liver metastases

Abbreviations: ACT, adjuvant chemotherapy; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CK, cytokeratin; EpCAM, epithelial cell adhesion molecules; F, female; GEM, gemcitabine; HBV, hepatitis B virus; HCV, hepatitis C virus; LD, lymph node dissection; M, male; ND, not described.

The patient was discharged on postoperative day 12 without any complications, and she was administered adjuvant chemotherapy with S-1. However, follow-up CT 6 months after surgery showed multiple liver metastases; therefore, the patients is now receiving systematic chemotherapy with gemcitabine.

3. Discussion

CoCC comprises mixed HCC and CCC components, and is categorized as a subtype of CCC based on World Health Organization (WHO) guidelines. The frequency of CoCC occurrence is 0.6–1% among primary liver tumors [1,2]. Recent histological and immunohistochemical findings have indicated that CoCC are derived from HPCs, which are liver-specific stem cells that can differentiate into hepatocytes and cholangiocytes [3]. Previous studies also showed that most patients with CoCC were infected with hepatitis B or C viruses, or else abused alcohol; inflammation caused by the viral infection is thought to be a risk factor for CoCC [3,8].

Characteristic radiological findings for CoCC are patchy enhancement patterns in the arterial phase; these enhanced effects are delayed in the equilibrium phase because of the abundant fibrous stroma of the tumor [6,11,12]. Some reports have described the imaging findings of CoCC to be very similar to those of CCC or HCC [2,13]. HCCs commonly show rapid homogeneous enhancement of the tumor that quickly washes out in the late phase [14]. On the other hand, CCC is characterized by a thin and mild peripheral enhancement on early-phase images that is due to an abundant fibrous stroma [15]. Previous studies demonstrated that the presence of a non-obstructed vessel within the tumor (without a capsule) as well as the absence of intratumoral necrosis were particularly characteristic of CoCC [7,13]. The mechanism of vessel penetration into a tumor was shown to have a replacing growth pattern rather than a compressive one [12]. Portal vein penetration into the tumor has been reported [12], and is commonly detected in malignant lymphoma or CCC [13]. On the other hand, the penetration of the hepatic artery into the tumor has not been previously reported. The difference between the feeding and penetrating arteries on CT is that the feeding artery appears to be involved with the tumor, and radially narrows so that it is undetectable on CT when it is in close proximity to the lesion. However, a penetrating artery persists after passing through the tumor and can be traced on CT. Hepatic artery penetration may therefore be an important finding in CoCC, and may represent a unique tumor growth pattern.

Pathological and immunohistological examinations are important for the diagnosis of CoCC. According to the WHO classification, the histologic features of CoCC include admixtures of small monotonous glands, antler-like or anastomosing patterns with abundant fibrous stroma, and cuboidal tumor cell that are smaller in size than normal hepatocytes. Immunohistochemical examination is also useful for the diagnosis of CoCC; because they were derived from HPCs, these tumor cells are positive for CD155, CD44, and EpCAM. Some studies reported that the biliary markers CK9 and CK19 were expressed in CoCCs [5]; the tumor in our case showed positivity for EpCAM, CK7, and CK19.

A list of reported patients with CoCC who underwent resection is shown in Table 1 [6,11,16–21]. CoCC exhibits less invasion to the portal vein as well as a lower number of intrahepatic metastases than CCC [8]. Therefore, patients with CoCC survived longer after surgery than those with CCC [3,8]. Tomioku et al. reported a patient who underwent repeated hepatectomy for recurrent intrahepatic CoCC [6]; hence, patients with solitary and metachronous liver recurrence may be candidates for curative resection. In fact, curative resection is the first choice for patients with CoCC. The prognosis and recurrence rates of CoCC are also unclear, although

a maximal tumor size of >40 mm was reported to be an independent risk factor for recurrence [3]. Despite receiving adjuvant chemotherapy, our patient, whose tumor had a maximum diameter of 60 mm, experienced early recurrence. The effect of chemotherapy in patients with CoCC remains unclear; further investigations are required to determine effective adjuvant chemotherapy regimens for this disease.

4. Conclusion

We reported a case of CoCC in a normal liver that exhibited penetration by the hepatic artery. Multiple liver recurrences occurred even after curative surgery. The tumor size, as well as the unique growth pattern that involved hepatic artery penetration through the tumor, appeared to be risk factors for recurrence.

Conflicts of interest

None.

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Informed consent

Written informed consent was obtained from the patient for the publication of this case report.

Author contributions

Hiroaki Yamane was involved in writing the article; Tomoyuki Abe designed the study and was involved in writing the article; and Hironobu Amano, Tsuyoshi Kobayashi, Keiji Hanada, Shuji Yonehara, Hideki Ohdan, Masahiro Nakahara, and Toshio Noriyuki provided critical intellectual input for the described work. All authors have approved the final version of this manuscript.

Ethical approval

Onomichi general hospital.

Guarantor

Tomoyuki Abe.

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